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AMINOPHYLLINE TOXICITY

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SINCE Trasoff,[1] Efron,[2] Herrmann and Aynesworth,[3] and Efron and Everett[4] first reported aminophylline to be effective in the treatment of bronchial asthma between 1933 and 1939, this drug has been used fairly extensively and commonly, because of its bronchodilating action, in the treatment of bronchial asthma and other allied conditions of bronchiolar obstruction in infants and children. Fortunately, the majority of pediatric patients appear to tolerate this drug and develop no untoward reactions. It is not generally appreciated, however, that aminophylline may cause varying degrees of toxic reactions and even death, due usually to overdosage of or possibly idiosynerasy to the drug. In view of the important fact that the early cardinal symptoms of aminophylline poisoning may be misinterpreted and attributed to the respiratory disorder which is being treated at the time, failure to discontinue this drug will cause a progressive and irreversible deterioration of the patient, characterized by restlessness, vomiting, convulsions, fever, respiratory paralysis, or vasomotor collapse and death.

Merrill[5] was the first to report three fatal reactions to the intravenous administration of aminophylline in adults in 1943. Bresniek and coauthors[6] reported three additional fatal reactions in adults following the intravenous administration of aminophylline in 1948. References pertaining to adverse reactions to aminophylline have appeared in the literature from time to time. Glaser[7] mentioned in 1946 that "adverse side effects such as nausea and vomiting which are not controlled by symptomatic treatment are indications for stopping the drug." Vaughan and Black[8] stated in 1948 that "injections (of aminophylline I.V.) should be given very slowly to avoid unpleasant symptoms such as flushing, weakness, palpitation and even collapse. A few deaths have been reported following I.V. use, but this is rare and should not prevent the use of this valuable drug." Schick and Peshkin,[9] in discussing the use of aminophylline, write that "reactions are common and mild, but occasionally unpleasant symptoms of acute vasomotor collapse with loss of radial

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pulse may ensue." Chobot[10] warns that "it must be given very slowly or side reactions such as palpitation and flushing, nausea, and vomiting occur." Overall[11] states that "if too large a dose or too rapid an injection is given, restlessness, tachycardia, extra-systoles, delirium, amblyopia and muscle tremors may ensue. Death has been reported during the time of injection." Cullen and Gross[12] advise aminophylline to be "injected very slowly, for rapid administration causes a precipitous drop in blood pressure." Unger and Unger[13] state that the "prime ill effect of aminophylline is nausea. An occasional patient exhibits faintness and collapse from too rapid I.V. administration." Levin[14] mentions that "a number of patients exhibit toxic symptoms from aminophylline, and one should guard against overdosage with this drug. The most frequent toxic symptom in our experience is nausea and vomiting. We have seen several children with peripheral vascular collapse from overdosage. At the earliest sign of any of these adverse effects, the drug should be discontinued."

The first fatality reported in the pediatric literature due to aminophylline poisoning (attributed by the authors in this case to the combined toxic effects of aminophylline and ephedrine) was by Gardner and associates[15] in 1950. Ensuing reports by Pioppi,[16] Frazier,[17] Rounds,[18] Love and Corrado,[19] Nolke,[20] and White and Daeschner[21] have revealed a total of thirty-one cases of aminophylline poisoning in the pediatric age range, eight of which have been fatal. It is highly probable that additional cases have not been reported because of clinical failure to recognize aminophylline as being the responsible and toxic agent involved in these cases.

This paper is being presented to report two more fatal cases of aminophylline poisoning (one of which is possibly due to combined aminophylline and ephedrine toxicity), to review the literature and the problem of dosage, and to stress the importance of the early clinical recognition of aminophylline toxicity.

CASE REPORTS

CASE 1.—This 3-year-old Puerto Rican boy was admitted to the hospital at 11:30 A.M. with a history of cough and respiratory difficulty of twenty-four hours' duration. The past history was noncontributory outside of an admission one year previously for "acute bronchitis" which necessitated a hospital stay for five days. He was seen at first in the emergency room, where an injection of Adrenalin was given and an x-ray of the lungs was taken (x-ray was reported as being negative other than increased markings at the hilar and basal areas of the lungs). Because of failure to improve after the injection of Adrenalin, hospitalization was advised.

Physical examination revealed a thin (12.2 kilograms), fairly well-developed boy, appearing acutely but not critically ill, dyspneic, somewhat anxious, with an audible expiratory wheeze. Temperature was 100° F., pulse 130 per minute, respirations 36 per minute. The lungs were filled with musical râles and wheezes and expiration were prolonged and difficult. The white blood cell count was 16,850 with 80 per cent polymorphonuclear leukocytes and 20 per cent lymphocytes. The urinanalysis was negative other than a trace of albumin.

The patient was placed in an oxygen tent, given an intramuscular injection of 300,000 units of aqueous procaine penicillin and 3½ grains (210 mg.) of aminophylline intramuscularly at 11:48 A.M. One dram of

syrup of ephedrine sulfate, N.F., was given a few minutes later (1 dram of syrup of ephedrine sulfate, N.F., equals ¼ grain or 15 mg.). At 6 P.M. the same day a suppository of 3½ grains (210 mg.) of aminophylline was also given. By the late evening the boy was less dyspneic, retained fluids, and was generally more comfortable. He slept fairly well that night. At 8 A.M. the next morning he was noted to be dyspneic again and very restless and apprehensive. Approximately twenty minutes after eating his breakfast, he vomited about 300 c.c. of "dark brown, viscid material." Throughout the afternoon and early evening he continued to be very restless, fretful, and apprehensive. The medications on this day consisted of an intramuscular injection of 300,000 units of aqueous procaine penicillin at 9 A.M., 1 dram of syrup of ephedrine sulfate at 8 A.M., 12 M., 4 P.M., and intramuscular injections of 3½ grains of aminophylline at 12 M. and 6 P.M. At 8 P.M. the patient had a generalized convulsion and vomited a large amount of dark brown material. Physical examination revealed a comatose child with tonic and clonic twitchings of the extremities and blood-tinged fluid on his lips. Temperature was 102° F., pulse was 140 per minute and of poor quality, and respirations were rapid and shallow. Coarse moist râles but no wheezes were heard throughout the lung fields. A catheterized urine specimen showed a trace of albumin, 3 plus acetone, a few red blood cells and numerous white blood cells per high-power field. One grain (60 mg.) of sodium phenobarbital was given intramuscularly at 8:15 P.M. and again at 9:45 P.M. Twitchings continued in spite of the anticonvulsant medication. A spinal tape was done at 9:30 P.M. (the restlessness, vomiting, twitchings, and convulsions were not recognized as being due to aminophylline toxicity). The spinal fluid findings were negative. Respirations became more shallow and rapid, blood pressure was unobtainable, and the patient died at 10:40 P.M.

This patient received one aminophylline suppository of 3½ grains (210 mg.) and three intramuscular injections of 3½ grains (210 mg.) each of aminophylline as his total dosage of this drug. The calculated dose was 17.2 mg. per kilogram of body weight. In addition he received a total of 1¼ grains (75 mg.) of ephedrine sulfate.

Autopsy Report.—The gross findings were essentially negative outside of the lungs and brain. They were reported as follows:

(1) Lungs. The bronchial tree showed the presence of an abundant mucopurulent exudate. The bronchial mucosa was slightly injected. Serial sections of the lung revealed a normal appearance. There was present a small area of consolidation in the right middle lobe. The remaining lobes of the lungs had essentially normal crepitation and appearance with the exception of the right lower lobe where crepitation was decreased. The left lung weighed 80 grams; the right lung, 110 grams.

(2) Brain. On opening the skull there was present severe cerebral edema with some injection of the superficial cortical vessels. The convolutions of the cortex were generally flattened. The meninges appeared normal. The vessels at the base of the brain showed no unusual features. The cerebral hemispheres were symmetrical. The cerebellum showed no unusual features. Serial sections revealed injection of the small vessels within the parenchyma, with suggestion of petechial hemorrhage. Ventricular system was symmetrical and showed no abnormalities. The brain weighed 1,350 grams.

Anatomical diagnosis: (1) pneumonia of right midlobe; (2) cerebral edema, severe.

CASE 2.—This 4-year-old Puerto Rican boy was admitted to the hospital with a history of forty-eight hours of cough and respiratory difficulty and fever of twenty-four hours'

duration. The patient was admitted three years previously for "acute bronchitis," which cleared after four days of antibiotic therapy. The parents stated that the child suffered from frequent colds and attacks of difficulty in breathing for the past two years. Physical examination revealed a thin (12.6 kilograms), acutely ill child in moderately severe respiratory distress, with labored, wheezing respirations. The lungs were full of musical râles and loud wheezes were heard on expiration. Temperature was 102.6° F.; pulse 128 per minute, respirations 48 per minute. He was put into an oxygen tent, given 3 minums of 1:1,000 Adrenalin subcutaneously, and an intramuscular injection of 300,000 units of aqueous penicillin. (Penicillin to be repeated every four hours for four injections. A suppository of 3¾ (225 mg.) grains of aminophylline was ordered. By mistake, a suppository of 7¾ grains (465 mg.) of aminophylline was given at 3:20 P.M. At 4:30 P.M. the patient became extremely restless and had to be removed from the oxygen tent. Small amounts of fluid were taken and retained. The boy was taken in and out of the oxygen tent in the following four to six hours because of marked restlessness and agitation. The wheezing became less pronounced by 11 P.M. of the same evening, but the restlessness and apprehension continued unabated. At 2 A.M. the following morning another suppository of 3¾ grains of aminophylline was given. The boy was noted to be dyspneic, pale, and extremely restless at this time (no vomiting was reported). At 9 A.M. the patient received the third rectal suppository of 3¾ grains of aminophylline. The temperature at 8 A.M. was 100.6° F. At 10 A.M. he had a generalized convulsion, respirations became rapid and shallow, and cyanosis developed. In spite of emergency measures, the patient died at 10:30 P.M. Permission was not granted for an autopsy.

This patient died nineteen hours after beginning aminophylline therapy. He received one aminophylline suppository of 7¾ grains (465 mg.) and two suppositories of 3¾ grains (225 mg.) each. The average dose of aminophylline was 24 mg. per kilogram of body weight.

DISCUSSION

Pharmacology and Toxicology.—Of the three best-known xanthine alkaloids, caffeine, theobromine, and theophylline, the last one is considered to be the most potent in relaxing smooth muscle. Since it is erratically absorbed from the gastrointestinal tract, theophylline can be made more effective by combining it with ethylenediamine. Thus aminophylline is actually theophylline solubilized by combination with ethylenediamine. The generic name is aminophylline, U.S.P. The chemical name is theophylline ethylenediamine. It contains not less than 75 per cent and not more than 82 per cent of anhydrous theophylline ($C_7 H_8 N_4 O_2$) and not less than 12.3 per cent and not more than 13.8 per cent of ethylenediamine ($C_2 H_8 N_2$).[22]

The main pharmacological actions of these xanthine derivatives (since all three are closely related in chemical structure and differ only in degree of effect on different organs, they will be considered together) with which we are concerned are as follows:[23]

(a) Central nervous system stimulation (cortex).

(b) Smooth muscle relaxation (bronchial mucosa, blood vessels).

(c) Cardiovascular and vasomotor stimulation.

(d) Diuretic action on kidneys.

Regarding the all-important toxicological effects, they are as follows:[23, 24]

(a) Central nervous system manifestations—headache, tinnitus, light

flashes, confusion, irritability, excitement, restlessness, generalized increase of reflex excitability, tonic and clonic convulsions.

(b) Gastrointestinal manifestations—nausea, vomiting, hematemesis due to gastric or intestinal hemorrhage (these symptoms can occur with oral as well as parenteral administration).

(c) Respiratory manifestations—respiratory failure due to spasm of the diaphragm or toxic effect on the respiratory center.

(d) Kidneys—albuminuria.

Since children are more sensitive to the effects of the xanthine drugs and their general reflex excitability is higher than adults, it is to be expected that any toxic reaction will be more severe in the pediatric age group than in adults.

Necropsy studies obtained in a certain number of cases have revealed the following significant findings:

(a) Esophageal, gastric, and duodenal ulcers with hemorrhage.[15, 24]

(b) Esophageal ulceration with perforation, ulcerative esophagitis with perforation into the mediastinum, and ulceration of the esophagus with erosion into the pleural cavities.[20]

(c) Petechial hemorrhages in the liver, spleen, and brain.[15]

(d) Cerebral edema (it is interesting to note that electroencephalograms obtained in three of Rounds'[18] cases were reported as showing "slow waves consistent with cerebral edema").

(e) Central lobular congestion of the liver, central necrosis.[20]

Clinical Manifestations of Aminophylline Poisoning.—

(1) *Restlessness:* The sine qua non of aminophylline toxicity is restlessness. This cardinal symptom may develop within a half hour to an hour following the institution of aminophylline therapy or may be delayed for a varying number of hours. This constant symptom is the earliest warning of danger. It is outstanding from the onset, becomes progressively more marked, and may even reach a stage of uncontrollable agitation, delirium, or mania. The development of restlessness should alert the physician at once as to the probability of aminophylline poisoning in any patient who is receiving this drug. Although some degree of restlessness may occur in a severe case of bronchial asthma, it does not compare with the extreme degree of restlessness seen in aminophylline poisoning.

(2) *Vomiting:* This practically constant symptom usually develops within minutes to hours after the onset of restlessness (occasionally preceding it), is frequent in occurrence, and may become intractable. In spite of the continued emeses, most patients appear to be thirsty and continue to take fluids but are unable to retain them. After a varying period of time, the vomitus becomes frankly bloody in appearance or resembles a "coffee-ground" or thick brown or brownish red fluid. Dehydration follows and its severity depends upon the frequency and duration of the vomiting. Although vomiting occurs fairly often during asthmatic attacks, it is rarely as frequent and rarely becomes bloody or "coffee-ground" in appearance as it does so frequently in cases due to aminophylline poisoning.

Thus the patient who is receiving aminophylline (no matter which route of administration is being used) for the treatment of bronchial asthma or any other type of respiratory ailment must be observed carefully and frequently. At the first sign of restlessness (or similar symptoms of central

nervous system stimulation—hyperirritability, hyperactivity, agitation, marked fretfulness, apprehension, etc.) which is the cardinal symptom of aminophylline toxicity, it is imperative to discontinue the drug at once. Almost concomitantly with or shortly after the onset of restlessness (or occasionally preceding it) vomiting develops. Frequent vomiting is another warning symptom which makes mandatory the immediate discontinuation of this drug. If one continues to administer aminophylline after the onset of these early symptoms (restlessness and vomiting), then the clinical picture progresses almost invariably and inexorably to one of severe agitation (some to delirium, stupor, or coma), vomiting of frankly bloody, "coffee-ground," or thick brown material, convulsions or twitchings (hyperthermia between 105° and 108° F. in some cases), respiratory paralyses or vasomotor collapse, and death.

(3) *Convulsions:* Convulsions occur in over 50 per cent of the cases. These may continue intermittently for hours despite anticonvulsant measures. In other cases muscular twitchings of the extremities or face may occur.

(4) *Fever:* In the majority of cases, moderate fever is present. This may be extreme and the temperature range between 105° and 108° F. In ten of the reported cases the temperature was 105° F. and above. In three cases it was 107.2° to 108° F.[18, 20] In some instances, however, the fever may be low grade or entirely absent.

(5) *Albuminuria:* In some cases a 1 plus to 4 plus albuminuria has been reported. This finding, however, has been an inconstant one.

The thirty-three patients reported in the literature ranged in age from 5 months to 6 years, with a mean age of 27 months. Twenty-seven patients were 3 years of age and under, with five of these being less than 1 year of age. Thus 82 per cent of the cases occurred in children 3 years of age and under and 64 per cent in children 2 years of age and under. Out of the thirty-three cases, the drug was administered rectally in twenty-four instances (over 72 per cent of the cases were due to the use of rectal suppositories), four patients received the drug intravenously and rectally, two orally and rectally, one intramuscularly and rectally, one intramuscularly, one intravenously. An analyses of the dosage given in the reported cases[15-21] reveal the following:

(a) Rectally—10 to 40 mg. per kilogram of body weight, with an average of 21 mg. per kilogram of body weight.

(b) Orally—83 to 90 mg. per kilogram of body weight (two patients received about 2.6 mg. per kilogram of body weight).

(c) Intravenously—6 to 7 mg. per kilogram of body weight.

(d) Intramuscularly—17 to 28 mg. per kilogram of body weight.

Of the thirty-three cases reported, there were ten deaths, a mortality rate of 30 per cent. In six of the ten fatal cases aminophylline was administered via rectal suppository, one fatal case orally, one intravenously, one intramuscularly and rectally, and one rectally and intravenously. Of the fatal cases, the ages of the patients ranged between 9½ months and 6 years, with seven patients 2 years of age and over (one baby's age was unknown, one was 9½ months old, one was 18 months, two were 2 years,

one was 3 years, one 3½ years, one 4 years, and two were 6 years of age). The dose which the six fatal cases received rectally varied between 15 and 40 mg. per kilogram of body weight, with an average of 22 mg. per kilogram of body weight. The oral dose given one patient who died was 83 mg. per kilogram of body weight. The dose, both intramuscularly and rectally, given another was 17.2 mg. per kilogram of body weight. Another patient who died received an unknown amount of aminophylline intravenously. In still another fatal case the drug was administered intravenously and rectally, 6 and 10 mg., respectively, per kilogram of body weight. Table I gives a summary of the dosage, route of administration, age and weight, other drugs used, and the deaths in the thirty-three reported cases.

Problem of Dosage.—The dosage of aminophylline usually prescribed for adults varies between 0.1 and 0.2 Gm. orally, 0.33 and 0.5 Gm. rectally, 0.2 and 0.5 Gm. intravenously, and 0.5 Gm. intramuscularly. Thus the maximally recommended dose is approximately 7 mg. per kilogram of body weight (average adult — 70 kilograms) given intravenously, intramuscularly, or rectally, and a little less than 3.0 mg. when given orally. The dosage suggested for infants and children by the pediatric textbooks and pediatric literature is, in general, vague and not directly related to age and body weight. Hughes[25] recommends ½ to 3 grains by mouth or rectally, two or three times daily as required. De Sanctis and Varga[26] recommend 0.3 to 0.5 Gm. orally every four hours, rectally 0.125 Gm. every 4 to 6 hours in infants, and 0.25 Gm. every 4 to 6 hours in older children. Dees[27] suggests rectally 0.1 to 0.25 Gm. suppository or instillation and 0.25 to 0.5 Gm. as a retention enema for older children. Unger and Unger[13] recommend 0.3 Gm. (5 grains) for children, dissolved in 20 c.c. (⅔ ounce) of tap water as a retention enema. Levin[14] states that "a child of 4 years or more can usually tolerate a suppository containing 0.25 Gm. (3¾ grains) repeated once or twice at three- to four-hour intervals. For a younger child this suppository can be slit lengthwise and half the dose inserted." Cullen and Gross[12] state that children may be given aminophylline suppositories containing 0.12 to 0.24 Gm. (2 to 4 grains), depending on age. Schick and Peshkin[9] mention the intravenous administration of the drug from 0.24 to 0.48 Gm. (3¾ to 7½ grains) in 100 c.c. or more of distilled water or glucose solution. It is thus seen that no specific dosage for age and weight is available for use on studying the aforementioned recommendations. Only three references were found which mentioned specific intravenous dosage. Glazer,[7] Dees,[27] and De Sanctis and Varga[26] recommended 0.006 Gm. intravenously per kilogram of body weight. A final search revealed a table in the *Textbook of Pediatrics*[28] which suggested the following: aminophylline (I.V.; P.O.; R.), 1 to 3 mg. per pound slowly, 60 to 300 mg. every four hours; 60 to 120 mg. for infants; 250 mg. for older children.

Since aminophylline is not as effective when given orally (and this route is precluded in vomiting), appears to be most toxic when given intravenously, and is painful and irritating to the tissues when given intramuscularly, the discussion will be limited

TABLE I. SUMMARY OF THE DOSAGE, ROUTE OF ADMINISTRATION, AGE AND WEIGHT, OTHER DRUGS USED, AND DEATHS IN THIRTY-FIVE INSTANCES OF AMINOPHYLLINE POISONING

AUTHOR	NO. OF CASES	AGE WEIGHT	DOSAGE OF AMINOPHYLLINE (MG./KG.)* AND ROUTE OF ADMINISTRATION				OTHER DRUGS	DEATHS
			RECTAL	I.M.	I.V.	ORAL		
Gardner, et al.[15]	1	2 yr. 12 kg.				83	Ephedrine Phenobarbital	+
Pioppi[16]	2	3½ yr. 15 kg.	17				Pentobarbital	–
		2 yr. 12 kg.	21				Pentobarbital	+
Frazier[17]	1	Baby ?	?				None	+
Rounds[18]	6	18 mo. 11 kg.			?		None	+
		16 mo. 10 kg.	25				None	–
		18 mo. 11 kg.	23		?		Epinephrine	–
		3 yr. 14 kg.	18				None	–
		3 yr. 14 kg.	?		7		None	–
		11 mo. 9 kg.		28			None	–
Love and Corrado[19]	4	15 mo.** 10 kg.	25		50		Phenobarbital	–
		16½ mo.** 10 kg.	25				Epinephrine Pentobarbital	–
		2 yr.† 12 kg.	21			2.6	Epinephrine Phenobarbital	–
		29 mo.† 13 kg.	20				Phenobarbital	–
		19 mo. 11 kg.	23				Phenobarbital	–
		2 yr. 12 kg.	21			2.7	Epinephrine Phenobarbital	–
Nolke[20]	13	2½ yr. 12.9 kg.	17				Epinephrine	–
		3½ yr. 13.6 kg.	16				None	+
		7 mo. 7.7 kg.	28				Epinephrine Ephedrine	–
		13 mo. 8.6 kg.	17‡				Ephedrine	–
		2 yr. 12 kg.	14				Ephedrine	–
		6 yr. 21.8 kg.	15				Ephedrine	+

TABLE I—CONT'D

AUTHOR	NO. OF CASES	AGE WEIGHT	DOSAGE OF AMINOPHYLLINE (MG./KG.)* AND ROUTE OF ADMINISTRATION				OTHER DRUGS	DEATHS
			RECTAL	I.M.	I.V.	ORAL		
		2 yr. 11.8 kg.	19				Epinephrine	–
		5 mo. 8.6 kg.	25				None	–
		2 yr. 13.8 kg.	11‡				Ephedrine	–
		6 yr. 21.8 kg.	10		6		Epinephrine	+
		3 yr. 12.2 kg.	12‡				Ephedrine	–
		9½ mo. 5.4 kg.	40				Epinephrine	+
		3 yr. 14.5 kg.	15				Epinephrine	–
White and Daeschner[21]	4	23 mo. 10.6 kg.				90	None	–
		18 mo. 6.8 kg.	36				Phenobarbital	–
		6 yr. 21.5 kg.	23				None	–
		7 mo. 8 kg.	?				Epinephrine	–
Soifer	2	3 yr. 12.2 kg.	17	17			Ephedrine Epinephrine	+
		4 yr. 12.6 kg.	24				Epinephrine	+

*Values arrived at from author's summary.
**Represents two different hospital admissions of the same patient.
†Represents two different hospital admissions of another patient.
‡Theophylline given in these cases. Value expressed as aminophylline by the author. (Aminophylline contains about 78 per cent theophylline.)

mainly to the rectal administration of this drug (in thirty-one out of the thirty-five reported instances aminophylline was administered in suppository form).

As a historical sideline, it was interesting to learn that aminophylline has been known for over fifty years. Musser[29] stated in 1928 that "reference to theophylline-ethylenediamine first appeared in the literature 22 years ago." (Musser referred to the article by Dessauer.[30]) As far back as 1932, Herlitz[31] recommended the use of caffeine derivative (combination of theobromine-calcium salicylate and theophylline) in the treatment of asthmatic bronchitis in children. Herrmann and Aynesworth[3] remarked in their article that "Freud[32] has used aminophylline successfully, by rectal administration, in infants with periodic breathing of capillary bronchitis, in pneumonias of childhood and in the periodic breathing of encephalitis, all of which are considered central

disturbances of respiration.'' Dees[33] in 1943 recommended that aminophylline suppositories (0.25 Gm.) should be used more often because of ease of administration and fewer reactions. Since vomiting precludes the oral use of the drug and because of the ease of administration in children, the suppository form has become popular and used very often.

The problem of dosage is unfortunately complicated by the factors of unpredictability of absorption and cumulative effect of this drug. This was shown very clearly by Waxler and Schack[34] in their studies of the absorption and excretion of aminophylline in adults. Some of their findings reveal:

(1) Significant blood levels of aminophylline following either oral, intravenous, intramuscular, or rectal administration.

(2) Complete unpredictability of rectal absorption. Many patients showed no appreciable blood level of aminophylline even five to six hours after the insertion of the suppository. Others showed high levels as early as four hours later and significant levels nine hours later.

(3) Intramuscular and intravenous administration. Immediate peak levels with persistence for seven to eight hours, a prolonged and cumulative effect with intramuscular administration.

Thus, in view of the unpredictability of the rectal absorption of the drug, the significant blood levels which may persist eight to nine hours or more, and its tendency to be cumulative in effect, it becomes extremely difficult to set up a rigid or specific dosage table.

In the cases where aminophylline was given rectally, the dosage ranged between 10 and 40 mg. per kilogram of body weight, with an average of 21 mg. per kilogram of body weight. This is much higher than the recommended rectal dose of 7 mg. per kilogram of body weight in adults. The dose which was given rectally in the fatal cases ranged between 15 and 40 mg. per kilogram of body weight, with an average of 22.0 mg. per kilogram of body weight—again a dose much higher than the recommended dose of 7 mg. per kilogram for adults.

Further confirmation of the necessity of using lower dosages in infants and children is borne out by Nolke[20] who reported thirteen cases of severe toxic reactions in children due to aminophylline suppositories, with four deaths (in one of these fatal cases aminophylline was given both intravenously and rectally). He states that ''Only the criteria of De Sanctis and Varga[26] (who suggest 0.125 Gm. rectally every four to six hours for infants and 0.25 Gm. every four to six hours for older children) could be applied to the case material. Eight patients in the group did not receive therapy in excess of their recommendations. The occurrence of such reactions with acceptable doses prompts a reconsideration of the standards of acceptability. This appears particularly applicable to the younger age group, since 10 of the 13 patients were 3 years of age or less.''

Since no established dosage is available at present, it would be advisable to give an amount well below the calculated figures which caused the toxic reactions in the reported cases. In the most recent article on aminophylline poisoning in which they give an excellent summary of the literature on this subject, White and Daeschner[21] suggest a dosage of 7.0 mg. per kilogram of body weight rectally (also

3.5 mg. per kilogram for intramuscular or intravenous therapy and 5.0 mg. per kilogram for oral therapy). In view of the severe reaction which occurred with a dose of 11 mg. per kilogram of body weight, and the fatality which resulted from a dose of 15 mg. per kilogram of body weight, it is felt that a dose of 5 mg. per kilogram of body weight would offer a greater margin of safety and still be clinically effective.

There is no doubt that overdosage was present in all the reported cases (10 to 40 mg. per kilogram of body weight) and exceeded the dose recommended for adults (7 mg. per kilogram of body weight). Yet there is another possible factor which may play a role in some of these cases of toxic reactions to aminophylline. That is the possibility of hypersensitivity or sensitivity to the drug. When we consider the thousands of aminophylline suppositories which are used annually in this country in infants and children in excess dosage and the large amount of aminophylline which is used both intravenously and rectally in adults, and then reflect upon the paucity of reports in the literature over the past thirteen years (since Merrills'[5] report in 1943) concerning toxic reactions (as previously stated, it is probable that additional cases have not been reported because of clinical failure to recognize aminophylline as being the toxic agent involved), it is reasonable to assume that the possibility of hypersensitivity is a real one. This is all the more reason for making the physician more careful when administering this drug.

Since the present suppository for use in children is definitely too high in content (250 mg.), it would decrease the possibility of overdosage if suppositories of 50 and 100 mg. strengths were made available.

AMINOPHYLLINE-EPHEDRINE SYNERGISM

Gardner and associates[15] reported the first fatal case of aminophylline poisoning in a child in 1950. This 2-year-old patient died about fifteen hours after ingesting seven or eight Tedral tablets (a proprietary preparation containing theophylline, ephedrine, and phenobarbital; total dosage contained in this amount of tablets was 1.0 Gm. of theophylline, 0.2 Gm. of ephedrine, and 0.065 Gm. of phenobarbital). The clinical picture was exactly like that delineated in the later literature—restlessness, twitchings, vomiting of dark brown material, convulsions, and respiratory arrest.

Since no specific data were available at that time concerning the toxic doses of ephedrine and theophylline, Gardner carried out a series of interesting experiments, utilizing mice, in an attempt to determine the toxicological levels of these two drugs. In the summary of their article, they state that "the toxicity of ephedrine is nearly tripled by the concomitant action of moderate doses of aminophylline (theophylline ethylenediamine). Conversely, the toxicity of aminophylline is nearly doubled by the concomitant action of moderate doses of ephedrine. Thus, mixtures of these drugs containing relatively high proportions of theophylline are markedly synergistic. Theophylline in high dosage may be potentially more dangerous than is commonly thought."

A review of the reported cases reveals that ephedrine together with aminophylline was given in eight cases. In the fatal case reported by Gardner and associates[15] 0.2 Gm. of ephedrine

(17 mg. per kilogram) was given. Six of the thirteen patients reported by Nolke[20] received ephedrine in addition to aminophylline. One of these six which received ephedrine died (Case 6). An unknown amount of ephedrine in oil, 1:1,000 was given in this case. Of the other five patients, Case 3 received ephedrine sulfate, 25 mg., for six doses (3.2 mg. per kilogram); Case 4 received 25 mg. of ephedrine hydrochloride for two doses (3 mg. per kilogram); Case 5 received 15 mg. of ephedrine sulfate for two doses (1.3 mg. per kilogram); Case 9 received 25 mg. of ephedrine hydrochloride for three doses (2 mg. per kilogram); Case 11 received 25 mg. of ephedrine hydrochloride for two doses (2 mg. per kilogram). Our patient who died received 15 mg. of ephedrine sulfate for five doses (1.2 mg. per kilogram).

It is not possible to state with certainty the exact toxic effects which the ephedrine had in these cases. But in view of the article by Gardner and co-authors,[15] in which they showed that the toxicity of aminophylline is definitely and markedly potentiated by ephedrine and vice versa, it would appear reasonable to conclude that the concomitant administration of these two drugs is contraindicated.

TREATMENT OF AMINOPHYLLINE POISONING

The treatment is purely symptomatic and involves the following:

(1) Immediate discontinuation of aminophylline—the most important step!

(2) Anticonvulsant measures.

(3) Antipyretic measures.

(4) Treatment of shock, if present.

(5) Restoring fluid and electrolyte balance.

(6) As a prophylactic measure, it would be wise to warn the parents of the possibility of a recurrence of symptoms if exposed to the drug again.

SUMMARY

1. To date, thirty-three cases of aminophylline toxicity in infants and children have been reported with ten deaths. The age range varied between 5 months and 6 years, with a mean age of 27 months. Eighty-two per cent of the cases occurred in children 3 years of age and under.

2. Aminophylline is a useful but a potentially toxic drug which may cause severe reactions or even death, due usually to overdosage of or possibly hypersensitivity to the drug.

3. The earliest and most constant symptom of toxicity is restlessness. The next important and almost constant symptom is frequent vomiting. The onset of restlessness alone, or with vomiting, calls for an immediate discontinuation of the drug. If the drug is continued in spite of these symptoms, the patient will almost invariably develop irreversible damage and die. The other symptoms of convulsions and fever develop in over 50 per cent of the cases. Albuminuria is an inconstant finding.

4. The simultaneous administration of aminophylline and ephedrine appears to be contraindicated.

5. A suggested dosage of aminophylline to be given rectally is 5.0 mg. per kilogram of body weight every eight hours.

6. In order to decrease the possibility of overdosage, aminophylline suppositories should be made available in 50 and 100 mg. strengths.

7. The treatment of aminophylline poisoning is purely symptomatic and involves the immediate discontinuation of the drug and the use of appropriate supportive measures.

ADDENDUM

After this paper was completed, Veum and Schwartz[35] reported four additional cases of aminophylline toxicity, with one death. To date, then, thirty-seven cases of aminophylline toxicity have been reported, with eleven deaths.

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MASSIVE SPASMS

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MASSIVE spasms are a type of convulsive seizure which occur fairly commonly in infants and small children. They often are not recognized as convulsive seizures and as a result their significance with respect to prognosis and management may be poorly understood. Indeed a massive spasm may not appear very impressive and may be interpreted as normally occurring "nervous jerks" or "colic." Close observation, however, discloses that massive spasms are more than a simple "nervous jerk" and in fact are characterized by sudden involvement of most of the body musculature in a contraction which persists for a fraction of a second to several seconds. Other terms used to describe these attacks include salaam convulsions, massive myoclonic jerks, lightning major seizures, jackknife attacks, Blitzkrampfe, and infantile spasms.

West[1] and Newnham[2] recorded the clinical features of these seizures before 1850. They described the typical pattern of an attack and the nearly invariable complication of mental retardation. Improvement in intellect was noted in periods of freedom from attacks. Hemiparesis was also present in some patients. In addition, the authors called attention to the fact that attacks may be precipitated by the "twilight" state and their association with other types of seizures, particularly head-nodding, drop, and generalized seizures.

French and German authors[3-6] made later reports and Lederer[5] noted dilatation of the ventricular system in a number of cases. More recent publications describe the electroencephalographic and other findings associated with this type of epilepsy.[7-13]

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CLINICAL FEATURES

The most striking and essential feature of a massive spasm is the lightning-like contraction of the body musculature for a fraction of a second to several seconds with sharp flexion of the head and trunk, adduction and flexion of the limbs. Less frequently the contraction is one of sudden extension, i.e., retraction of head, arching of back, extension of lower limbs, extension and abduction of upper limbs. Another conspicuous feature of massive spasms is their tendency to occur in series with diminishing severity.

A cry, laughter, pallor, flushing, cyanosis, sweating, pupillary dilatation, and conjugate deviation or nystagmoid movements of the eyes may accompany a massive spasm, and the more severe attacks are followed by listlessness and drowsiness. A number of factors seem to provoke an attack, particularly the twilight state between

sleep and wakefulness, infection, sudden noise, feeding, handling, and excessive environmental heat.

Massive spasms appear as early as 2 days of age and as late as early childhood, although the usual onset occurs between 1 and 6 months of age. Spasms of this type may also be preceded or accompanied by other types of seizures, and the pattern may change from flexor to mixed or extensor. Massive spasms may cease without apparent cause for several days or weeks, rarely months, and then recur. When seizures cease for a period longer than this they are not likely to recur, although seizures of other types (focal, akinetic, or generalized) may begin.

At the onset or shortly thereafter, patients with massive spasms usually show evidence of mental deterioration and impaired motor development. When seizures become more frequent, the infants are often irritable, with periods of muscle rigidity, opisthotonus, and slight quivering of the limbs.

Examination usually discloses mental dullness and motor retardation. In addition there may be hemiparesis, choreoathetosis, increased muscle tone, unusually small head circumference, nystagmus, and strabismus.

LABORATORY FEATURES

The electroencephalogram is usually remarkably abnormal. The most consistent pattern is one of "hypsarhythmia," a term which refers to an electrograph that is diffusely and continuously abnormal with bursts of high-voltage generalized slow activity followed often by periods of electrographic silence and shifting foci of spike activity. On occasions, the electrograph shows only generalized slow spike and wave abnormalities and spike or sharp wave foci. Rarely the electroencephalogram is normal in a patient who is having clinical spasms.

Pneumoencephalograms usually show cerebral or cortical atrophy or both. Chemical studies of the blood and cerebrospinal fluid show no significant abnormalities.

PATHOGENESIS

This type of seizure appears to be a manifestation of severe cerebral damage in the young pediatric subject. The character of neurological signs, the degree of mental retardation, and the strikingly abnormal electroencephalographic pattern indicate that the damage to the brain is often severe and widespread. Causes of brain damage may be traced to the prenatal, perinatal, or postnatal periods and include also developmental anomalies, infection, anoxia, trauma, and metabolic disorders. It is often difficult, however, to determine the precise cause, and in approximately one-third of our subjects no definite etiology for the infant's cerebral damage is recognized.

PROGNOSIS

Prognosis is good with respect to cessation of massive spasms. However, over 15 per cent of patients have other types of seizures (focal, generalized, or akinetic) or develop them after the massive spasms cease. The severe mental deterioration represents a most serious aspect with respect to prognosis. Intellectual ability may improve after spasms cease entirely but it seldom returns completely to normal. Some children remain severely spastic and critically handicapped, and a few die of inanition and respiratory infection.

A more favorable prognosis with respect to mental development exists when seizures continue only for short periods. In such instances the underlying cerebral disorder is probably less profound. Patients whose massive spasms occur singly rather than in series also tend to carry a better prognosis.

The clinical picture presented by patients with massive spasms may be quite variable. Five cases are presented as typical examples.

CASE REPORTS

CASE 1.—C. D. B. (No. B-746) was one of monozygotic twins born to a 16-year-old primipara. The membranes ruptured spontaneously nineteen hours before delivery, about one month prior to the date of confinement. With spinal anesthesia female twins were delivered; one (the patient) weighed 2 pounds 3 ounces at birth and the sibling 3 pounds. Early in the neonatal period numerous cyanotic episodes occurred, and the patient required oxygen for eight days. Weight was 5 pounds at 2½ months of age. Her motor development was as follows: she rolled over at 3 months, attained head control at 4 months, sat alone at 7 months, crawled at 8 months, and pulled up at 9 months. She had a number of febrile ear infections without drainage. Family history of a maternal uncle who had epilepsy was recorded.

At 9 months of age she began to have momentary "spells" which were characterized by opisthotonus, extension of the arms, and staring. Occasionally several such attacks would occur one after the other. Crying often followed such an attack. Urinary incontinence and sometimes sleep for two to three hours after an attack were noted.

At the time of onset of seizures she was being treated for an ear infection. The seizures recurred despite therapy with elixir of phenobarbital. Soon after onset of the seizures she lost the ability to crawl and to sit.

Examination at 10 months of age showed definite motor and mental retardation. She was able to sit only with support. No specific muscle weakness was detected; evaluation of deep reflexes was unsatisfactory. The plantar responses were flexor. Response to painful stimulation appeared normal.

Hemoglobin was 8.6 grams per 100 c.c.; red blood count was 3.9 million; white blood count was 9,200, with 28 per cent polymorphonuclears, 65 per cent lymphocytes, and 6 per cent monocytes. Urinalysis, blood sugar, and blood urea nitrogen were within normal limits. Skull films revealed no abnormality. An electroencephalogram showed the typical pattern of hypsarhythmia, with some activity approaching normal in sections of the electrograph.

She was given Tridione, 150 mg. twice daily. Seizures diminished from six to three series daily. Each episode was made up of about thirty extensor spasms. Medication was changed to Gemonil, 25 mg. four times daily, and Mebaral, 16 mg. twice daily. Two seizures occurred the following day, but thereafter she was free of attacks for one and one-half months. A second electroencephalogram two weeks after the spasms ceased showed absence of the previously recorded hypsarhythmic pattern. There was much fast activity in both the waking and sleep records, but otherwise the electrograph was not remarkable.

When the dysrhythmia was under control and the seizures ceased, she began to improve with respect to motor and mental development. In fact, her behavior is considered superior to that of her twin. She has been free of seizures for eleven months.

CASE 2.—G. B. K. (No. A-824) was the second born of a 26-year-old mother. The pregnancy was complicated by vaginal bleeding for twelve hours at 6 months' gestation. The patient was born about two weeks beyond the expected date of delivery.

Presentation was cephalic and delivery spontaneous. Birth weight was 8 pounds 6 ounces.

He suckled normally, developed head control at 5 to 6 weeks, and then lost it at 3 months. He smiled at 2 months. He rolled over at 10 months, regained head control at 11 months, and sat alone at 12 months. He cooed and began watching things at about 11 months.

The first DPT immunization was given at 3 months, and was followed by high fever, lethargy, and refusal to move the left (injected) arm for three days. Since that date he had "jackknife" attacks.

The first seizure was characterized by sudden "jackknifing" of the body, that is, the thighs flexed, the legs extended, and the head, neck, and shoulders flexed forward. This posture lasted a second or two and then he relaxed. Flexor spasms recurred every 15 to 30 seconds for four to fourteen times. The eyes would roll back and on occasions he cried out. Following a seizure he might grin, and later would sleep for about two hours.

Initially the seizures had no apparent relation to the time of day; then with some consistency they occurred one or two hours after a bottle feeding. From 8 months of age, attacks occurred about 10 to 30 minutes after he fell asleep, regardless of the time he went to sleep. At 12 months of age the attacks decreased to one to two a day, and he began to use his left hand more.

Medications at various times included phenobarbital, with some decrease in the frequency of the attacks but with excessive lethargy. Dilantin was ineffective, but Tridione resulted in slight improvement. No medication was given from 12 to 14 months of age.

At 14 months the head circumference was 18¾ inches. His mental and motor development was approximately that of a 6- to 7-month-old infant. An electroencephalogram showed a paroxysmal generalized slow wave and spike and wave dysrhythmia; in addition, focal slow activity was present in the right temporal region.

Seizures ceased for three weeks after Mebaral and Gemonil were begun. Seizures then recurred once every other day. In addition, when sitting, his head would snap forward and arms throw out and upward with flexion of the legs. These spasms occurred in rapid succession and each contraction lasted 2 to 3 seconds with several seconds of relaxation between spasms. Fourteen to twenty spasms occurred in a series, after which he appeared very fatigued. Medication was changed to Dilantin and Gemonil, and two weeks later the seizures stopped. General motor and mental function improved. At 17 months of age the electroencephalogram was essentially the same but with less epileptiform activity during the waking state. A month later the epileptiform activity was no longer present, and the main pattern consisted of excessive high-voltage fast activity during sleep. A month later he walked with support and at 27 months he walked alone. Medication was then discontinued. Drooling stopped at 41 months. Although he was hyperactive, he could say a few words.

Examination at 43 months revealed constant motor activity, grinding of teeth, and placing what he could in his mouth. No motor weakness was noted. The extremities were slightly hypotonic. Tendon reflexes were slightly more active on the left. The plantar responses were flexor. The intellectual development was estimated to be 50 per cent of normal.

He was placed in a preschool class for retarded children. Coordination improved slightly and at 5½ years he could copy a straight line and a circle.

CASE 3.—R. P. H. (No. B-380) was a male child delivered at term. At 1½ months of gestation, brown vaginal spotting occurred for a day or two. The mother gained 35 pounds during pregnancy and was anemic. Fetal movements were noted during the last two months of pregnancy, but they

seemed "large and sluggish." Labor lasted four hours and the infant was delivered spontaneously. Birth weight was 5 pounds 10 ounces. The placenta was green and described as being the size of the mother's hand. The cord was small (the size of a pencil) and olive green. On account of difficulty in resuscitation, he was given oxygen and placed in an incubator. During a feeding attempt at 24 hours of age, he stopped breathing and became cyanotic. Two similar spells occurred.

Twitching of the right leg was noted during the first 3 months of life. Wakeful crying spells during the night occurred at 11 months. A month later, frequent episodes of sudden dropping of the head forward were noted. Head noddings continued, and at 14 months he began to have attacks for several seconds during which his face appeared "masklike" and he seemed unconscious.

Later the head nodding and face "stiffening" were associated with rigid forward throwing of the arms and loss of consciousness. These seizures lasted 3 to 60 seconds and occurred frequently after awakening in the morning and from naps. They also occurred about 2:00 A.M., waking the child and causing him to cry out. Phenobarbital caused some reduction in the number of attacks. Mebaral was not helpful.

Head control developed before 3 months. He rolled over at 12 months, sat alone at 14 months, crawled at 14 months, and walked at 16 months.

At 17 months the head circumference was 17½ inches. The fontanels were closed. Musculature was flabby and motor strength diminished. Movements were awkward and gait was unsteady on a broad base. Tendon reflexes were active and equal. He was retarded.

An electroencephalogram at this time was continuously epileptiform and diffusely abnormal (hypsarhythmia).

Tridione and Mebaral were begun. Tridione was later discontinued because of granulocytopenia and increasing frequency of seizures. Attacks then were characterized by stiffening of the neck, head nodding, or drawing up of the whole body. Most attacks were momentary, but some lasted 30 seconds. Mysoline was added to the Mebaral but about twenty seizures persisted daily. A combination of Milontin and Mebaral was tried but had no effect on the spasms. Two months later, medication was discontinued by the mother without change. Medication was later resumed. At 2 years 3 months he was less active. Flexor and massive extensor spasms continued and, in addition, he developed other seizures in which the left arm and leg jerked, he cried out, and the eyes rolled up with quivering of the eyelids and chin. Following these attacks, which lasted 2 to 3 minutes, he appeared fatigued.

Mebaral and Gemonil were then started and the seizures decreased in frequency. While awake, the attacks were characterized by twisting of the mouth, rolling up of eyes, flickering of eyelids, flexion of arms and legs, and "jackknifing" of the trunk. These lasted 15 to 90 seconds. During sleep, the attacks consisted only of mild flexion of the arms and legs. At 2 years 5 months of age he could hold a fork, throw a ball, and climb stairs. Increased motor and mental ability paralleled a marked decrease in number of seizures.

Seizures stopped for two and one-half months but later recurred, with momentary stiffening of the neck and approximately two brief head-nodding attacks daily. There were also episodes in which he would slowly fall. The dosage of Gemonil was increased.

CASE 4.—E. L. W. (No. B-408) was blue and cold at birth and given oxygen for three to four days. The mother had profuse placental hemorrhage for about an hour before delivery.

At 2 months of age, while going to sleep, twitching of one or another limb was noted. Occasionally all extremities jerked simultaneously. This occurred about twenty times daily and persisted for one month.

At 3½ months, while receiving ether anesthesia for circumcision, he became cyanotic for about five minutes in spite of oxygen. Circumcision was not performed, although urethral dilatation as carried out because of a history of straining with urination. Three days later he began to have spasms, which at first were slight but later became more severe and frequent. These consisted of flexion of the head and the upper limbs and occasionally of the legs. More severe attacks were accompanied by grunting. The attacks occurred in groups of ten to twenty each. Phenobarbital caused slight reduction in their frequency and severity.

At 4 months of age the head circumference was 16¾ inches. Head control was absent. He did not follow light. All limbs moved continuously. No reflex or sensory abnormality was noted. The following seizures were witnessed. Suddenly the head and arms flexed and within a moment the head and arms extended, with eyes turned to one side. The attacks lasted 2 to 3 seconds, and during more severe contractions he cried out.

An electroencephalogram at 4 months was grossly abnormal, with continuously epileptiform activity (hypsarhythmia). Dilantin was added to the phenobarbital therapy without success. Before an attack, he squirmed and fidgeted. The massive flexion spasm was accompanied by vertical movements of the eyes. More spells occurred on awakening and on falling asleep. With addition of Milontin, seizures continued unabated with series of sudden extension movements of the head ten to fifteen times in succession upon awakening. Doriden was substituted for Milontin. More seizures developed and therapy was reverted to phenobarbital, Dilantin, and Milontin. Two to twenty seizures occurred daily. At 1 year of age he did not laugh or smile. Head circumference was 43 cm. and head control was absent. Tridione was substituted for Milontin without significant change in number of seizures.

With Dilantin, phenobarbital, and Tridione he had sixty to 140 spasms daily which were now characterized by sudden extensor movements followed by "doubling up." He cried with each spasm. They lasted 2 to 5 seconds and occurred up to thirty times in one series. The head and eyes turned to the right in most attacks.

With a combination of Gemonil and Mebaral he had six to eight spasms per series. The electroencephalogram at 17 months of age showed essentially the same pattern as before. Seizures became less severe and decreased to two to three attacks per series. The total number of spasms varied between ten and fifty a day. His head tended to hyperextend. The addition of pyridoxine did not help. Spasms later increased to fifty to seventy daily. Medication was later changed to phenobarbital and Dilantin, and Milontin was added when he was 1¾ years of age.

CASE 5.—H. L. T. (No. B-495) was born of the mother's second pregnancy. She had severe headaches during the first months of gestation and severe uterine bleeding the second month. Delivery was a few days after term. Labor was induced by artificial rupture of membranes and lasted three to four hours. Forceps were used with "saddle-block" and intravenous Evipan anesthesia. Birth weight was 8 pounds 5 ounces.

The infant was very blue after delivery. The eyelids were swollen and the head bruised.

On the second day while the infant was trying to nurse, the left arm and leg extended and the left hand clenched for a half-minute or so. These "drawing spells" occurred during each feeding.

On the sixth day he had an attack in which the left limbs extended, the head and eyes turned to the left, and the left eye twitched rhythmically. Rhythmic jerkings of all extremities followed, with drooling of saliva and urination. The attack lasted 30 to 60 seconds. About ten similar seizures

occurred the same night and the following day. Phenobarbital was prescribed but fifteen to twenty seizures persisted daily. At 2 months of age Dilantin was started and seizures became less severe. About once every two weeks he had other attacks in which the head arched backward, the extremities "drew up," and cyanosis developed. These attacks lasted ½ to 1 minute.

He nursed well but slept a great deal. At 3 months he did not have head control and drooled excessively.

At 3 months the head circumference was 16⅛ inches. Tone was increased in all limbs, with tightness of the thigh adductors. The Moro reflex was weak and the grasp reflex was absent.

An electroencephalogram showed hypsarhythmia. During the electroencephalogram two types of seizures were observed: in one the head jerked suddenly forward on the chest and the arms made several massive jerks forward; in the other type, the arms slowly raised above the head, the head not moving.

An x-ray of the skull disclosed no abnormality. On phenobarbital and Mesantoin, a rash developed, and Mesantoin was discontinued. Dilantin, phenobarbital, and Diamox were started. He did well for a week, but seizures recurred. A combination of Tridione and Gemonil was then tried, but he had intermittent short, shaking movements of one hand and then the other. The feet also were involved on occasions.

At 4 months he was irritable and thrashed about. There was external strabismus and the patient assumed an opisthotonic position. He had no head control. Striking increase in tone of the lower limbs and slight increase in tone of the upper limbs were noted. Tendon reflexes were moderately increased, with unsustained clonus at the knee and ankle. Tonic neck reflexes were obtained to either side.

Pneumoencephalography showed slight general ventricular dilatation. Phenurone produced granulocytopenia and was discontinued. He then developed a new seizure pattern in which the arms and legs suddenly extended and there was a tendency for the head and trunk to turn to the right. Five to six of these attacks occurred daily. Milontin and phenobarbital were then prescribed. He did well for a few days and then became very hyperactive. He assumed an almost continuous position of opisthotonus. There were also momentary spells of sudden arching of the back, extension of the limbs, and turning of the head to the right. These occurred about seventy-five times daily. Doriden was then given, with reduction in seizures and with less opisthotonus. The drug was stopped for eighteen hours in order to test its efficacy and he again became opisthotonic, with continuous screaming and sudden extensor spasms. Doriden was reinstituted and he became quieter with fewer seizures.

At 7 months of age he had attacks in which he would cry out, hold his breath, and move both arms and either leg up. His head might pull back in an attack. The attacks occurred in series of five to six, usually once daily. He still had no head control and did not blink to threat stimuli. Thumbs were kept flexed into his palms. Head circumference then was 17¼ inches. Gemonil was attempted again but was ineffective, and the Doriden was reinstituted.

A repeat electroencephalogram at 8 months showed a mixed fast and slow dysrhythmia awake and excessive fast activity in sleep.

At 10 months of age he still had five to ten groups of spasms daily. He cried much of the time when awake and kept his head hyperextended and his legs stiff. Dilantin was attempted once more but he did no better, and a combination of Doriden and Gemonil was given. The mother later discontinued the Gemonil and varied the dosage of Doriden according to the severity of the seizures. At 12 months his condition remained unimproved. Pyridoxine was given orally, but the

mother thought it made him more irritable and that he was having more seizures, so it was stopped.

At 14 months of age, he was still having four to six seizures in series in the morning. In these his head would turn back to the right and his right arm and leg would flex while his left limbs would extend. Each spasm lasted 10 to 20 seconds, and seizures occurred in series. The mother was attempting to regulate the dosage of Doriden so as to obtain best seizure control without causing excessive drowsiness. The patient deteriorated slowly.

At 18 months of age, he had to be tube fed. Seizures occurred almost constantly while awake. The seizures consisted of crying, retraction of head, stiffening of legs backward, and spreading of the arms out. The attacks then lasted much longer but still occurred in series. In the meantime the patient began to run high fever without apparent cause. Electroencephalogram at this time showed continuous irregular high-voltage slow waves with irregular fast activity and irregular spikes in the occipital leads.

At 19 months of age he became cyanotic, extremely hot, and had gasping respiration. Oxygen and stimulants failed to revive him. He died out of town and an autopsy was not performed.

THERAPY

Massive spasms are conspicuously difficult to control. As in other forms of symptomatic epilepsy that are difficult to manage, it is often necessary to use a number of different anticonvulsant drugs before the most effective combination is found. In our experience Gemonil and Mebaral used together is generally the most effective medication. Dilantin, phenobarbital, Phenurone, Tridione, and Milontin may be of occasional usefulness. In some patients no drug or combination of drugs appears effective.

DIFFERENTIAL DIAGNOSIS

The occurrence of a loud and often distressing cry with a sudden massive flexion may be interpreted as intestinal colic (milk intolerance, intestinal obstruction, etc.). Impaired consciousness, conjugate deviation of the eyes and the history of attacks in consecutive series should, however, direct one's attention to impaired function in the central nervous system. Massive spasms may also simulate an exaggerated Moro reflex and the unusually brisk myoclonic responses sometimes seen in normal infants. Massive spasms occur spontaneously without external stimulation and often in series, thus differing from the typical Moro reflex. Ordinary myoclonic epilepsy does not appear until a later age, has less severe muscular contractions, and its electroencephalographic pattern is distinctly different. The extensor type of massive spasm may be confused with decerebrate attacks caused by increased intracranial pressure with herniation of the brain stem. In true decerebrate attacks the extensor contractions develop more slowly than that in massive spasms. In addition, the typical position of the arms in a decerebrate attack is one of extension and adduction, whereas in massive spasms it is one of extension and abduction.

SUMMARY

Massive spasms form a type of seizure occurring in infancy and early childhood. They are characterized by sudden contraction of most of the body musculature, the usual pattern involving flexion and adduction of the upper limbs, and flexion of the trunk and lower limbs. The attacks often occur in series. Other types of seizures,

such as head-nodding, and akinetic and generalized attacks are frequently associated with the massive spasms.

Motor and mental retardation often parallel the severity of the seizures. The electroencephalogram usually reveals the grossly and continuously abnormal pattern of hypsarhythmia. Pneumoencephalography shows ventricular dilatation.

Massive spasms are difficult to control by medication. A combination of Gemonil and Mebaral has proved to be the most generally effective anticonvulsant therapy. The massive spasms usually disappear after several months, but the patient may then develop other types of seizures.

Although some improvement of mental ability is common upon cessation of the spasms, recovery to normal mentality is unusual.

The differential diagnosis is discussed. Five case histories are presented to illustrate the features of this form of epilepsy.

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BR-R-R-R-R

September 24, 1754. My wife dipps little John [14 months old] into Cold Water to cure him of his Ricketts. 25th. John was dippd again. . . . 26th John was dippd again, and we cease for a while. . . . October 2. William takes his mother to Mrs. Martyns, and Lucy undertakes to wean little John. . . . Sent Billy to Mr. Garfield for pursley water for little John. . . . 26th A cool Morning after the Storm. My Wife goes on in plunging little John in Cold Water. . . . 27th John dipd again. . . . November 5 We have reason to fear little John is much troubled with Worms as well as Rickets, and is much oppressed having very labouring Breath. May God teach us to profit by his holy Hand upon us.

REV. EBENEZER PARKMAN DIARY.

A STUDY OF ACUTE RESPIRATORY DISEASE IN INFANCY

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THIS paper presents the results of the first two years of a continual investigation into the problems of acute respiratory disease in young children, with particular reference to bacteriological studies and an appraisal of the efficacy of a variety of antibacterial agents.

METHOD

During two six-month periods throughout the winter months of 1953-1954 and 1954-1955, 100 infants 3 years of age or under, suffering from respiratory infections sufficiently severe to require hospitalization, were studied. For the purpose of this study, respiratory infection was defined as any acute inflammatory process involving the nose, throat, middle ear, trachea, bronchi, and lungs. Excluded from this definition were infants suffering from severe epidemic laryngotracheobronchitis, pulmonary tuberculosis, and respiratory allergies.

In the first six-month period, forty infants were studied. By a method of predetermined selection they were allocated to one of two therapeutic groups. Each group consisted of twenty infants. One group received treatment with a suspension of sulfamethazine containing 0.5 Gm. per 5 ml.; the other group received a similar suspension of sulfamethazine to which had been added 150,000 I.U. of dipenicillin G dibenzylethylene diamine per 5 ml. Both preparations were administered orally, every six hours in a dose of 1.0 ml. per pound per day. Thus the first group received 0.1 Gm. per pound per day of sulfamethazine, while the second group received this dose of sulfamethazine plus 30,000 I.U. per pound per day of dipenicillin G dibenzylethylene diamine.

In the second six-month period sixty infants were studied, and by a method of predetermined selection they were allocated to one of three therapeutic groups. Each group consisted of twenty patients. One group received an oral drop preparation of chlortetracycline (Aureomycin) which was administered every six hours in a dose of 10 mg. per pound per day. The second group received oxytetracycline (Terramycin), also as an oral drop preparation administered in the same dosage. The third group received tetracycline (Achromycin) administered in the same form and dosage as the preceding groups.

The decision to discontinue the chosen therapeutic agent was arrived at in each individual case by an assessment of the whole clinical picture.

At the time of admission a complete history and physical examination were carried out on each patient. Routine investigation consisted of a culture of

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the nasopharynx, an x-ray of the chest, a hemoglobin estimation, a total and differential leukocyte count, urinalysis, and a tuberculin patch test. In the majority of cases the nasopharyngeal culture was repeated daily until the cessation of treatment. Urinalysis was repeated daily in the patients receiving sulfamethazine. Pulse, rectal temperature, and respiratory rate were recorded every six hours in all patients. Each patient was examined daily by one or more of the investigators.

All the patients belonged to the same socioeconomic group, and they were all admitted to the public service of the same ward of the hospital.

Comparison of the Constitution of the Therapeutic Groups.—Of critical importance in the evaluation of the results was the extent to which the five groups of patients were similar in certain basic characteristics. To confirm that the randomized allocation of patients to therapeutic groups had achieved this similarity, the following analyses were applied.

Sex distribution, age, weight, leukocyte count, temperature, and hemoglobin on admission to hospital were the basic characteristics selected from each group. Statistical analysis by the methods of variance showed that, with the exception of minor differences in sex distribution, the five therapeutic groups were similar in regard to the selected basic characteristics (Table I).

TABLE I. THE INCIDENCE OF BASIC CHARACTERISTICS IN EACH THERAPEUTIC GROUP

		SULFA	SULFA AND PENICILLIN	CHLOR-TETRA-CYCLINE	OXYTETRA-CYCLINE	TETRA-CYCLINE
Sex	Male	13	9	13	12	7
	Female	7	11	7	8	13
Age in months	Mean	13.8	12.8	13.8	12.7	14.1
	Range	0.5-33.0	2.5-24.0	3.0-32.0	2.0-42.0	4.0-25.0
	S. D.	2.70	2.94	3.09	3.39	2.35
Weight in ounces	Mean	324	336	327	305	313
	Range	131-512	119-496	162-480	91-536	140-507
	S. D.	27.3	30.3	30.2	40.8	28.6
W. B. C. in thousands per cu. mm.	Mean	15.6	12.4	13.2	13.4	13.6
	Range	6.0-30.0	4.2-25.4	7.3-28.0	3.4-36.1	7.6-24.5
	S. D.	8.14	5.70	4.77	7.67	4.11
Temperature on admission (°F.)	Mean	102.5	102.8	101.8	101.8	102.8
	Range	99.0-104.4	99.2-106.0	99.4-104.2	98.4-105.0	99.4-104.8
	S. D.	1.74	1.70	1.73	3.07	1.41
Hemoglobin in Gm. per cent	Mean	11.2	10.8	10.7	10.6	11.4
	Range	7.2-13.2	7.0-14.0	5.8-13.6	5.1-14.2	8.4-15.0
	S. D.	2.32	2.25	2.12	2.05	3.44

An anatomical-bacteriological diagnosis was made on each patient and compared according to the therapeutic groups (Table II). In some infants there was more than one site of disease. Thus nasopharyngitis, otitis media, and pneumonia were often combined in the same patient. Where this situation arose, a major anatomical diagnosis was made, by giving pneumonia precedence over bronchitis, bronchitis precedence over tonsillitis, tonsillitis precedence over otitis media, and otitis media precedence over nasopharyngitis. Thus only one major anatomical diagnosis was recorded for each patient in Table II.

TABLE II. ASSOCIATION BETWEEN BACTERIOLOGY AND MAJOR ANATOMICAL DIAGNOSIS FOR EACH PATIENT IN EACH THERAPEUTIC GROUP

	SULFA	SULFA AND PENICILLIN	CHLORTETRACYCLINE	OXYTETRACYCLINE	TETRACYCLINE
Nasopharyngitis (10 per cent)	1 *H. influenzae* 1 N.P.O.	1 Pneumococcus	1 Pneumococcus 2 N. P. O.	1 Pneumococcus 1 N. P. O.	1 Pneumococcus 1 N. P. O.
Otitis media (21 per cent)	1 Pneumococcus 1 *Staph. aureus*	2 Pneumococcus 1 Beta hemolytic streptococcus	2 Pneumococcus 1 *Staph. aureus*	1 Pneumococcus 1 *Staph. aureus*	1 *Staph. aureus* 1 Beta hemolytic streptococcus
	2 N. P. O.	1 N. P. O.	2 N. P. O.	2 N. P. O.	1 *H. influenzae* 1 N. P. O.
Tonsillitis (8 per cent)	1 Pneumococcus 1 Beta hemolytic streptococcus	1 *Staph. aureus*		2 Pneumococcus	
	1 N. P. O.	1 N. P. O.			1 N. P. O.
Bronchitis (22 per cent)	3 Pneumococcus 1 Beta hemolytic streptococcus	1 Pneumococcus 1 *Staph. aureus* 1 *H. influenzae*		4 Pneumococcus	3 Pneumococcus
		3 N. P. O.	2 N. P. O.	1 N. P. O.	1 *H. influenzae* 1 N. P. O.
Pneumonia (39 per cent)	3 Pneumococcus 2 *Staph. aureus*	2 Pneumococcus 1 *Staph. aureus* 1 Beta hemolytic streptococcus	2 Pneumococcus 2 *Staph. aureus*	3 Pneumococcus 1 Beta hemolytic streptococcus	3 Pneumococcus 1 *Staph. aureus*
	1 *H. influenzae* 1 N. P. O.	1 *H. influenzae* 2 N. P. O.	6 N. P. O.	1 *H. influenzae* 2 N. P. O.	1 *H. influenzae* 3 N. P. O.
	20	20	20	20	20

Pneumococcus, 37%; *Staph. aureus*, 12%; *H. influenzae*, 8% beta hemolytic streptococcus, 6%; no pathogenic organisms (N.P.O.), 37%.

Similarly an attempt was made to establish a single bacteriological diagnosis for each patient. The responsible organism was usually considered to be that which grew most profusely on the first or second nasopharyngeal swab. In certain cases of doubt where more than one potentially pathogenic organism was cultured from the same swab, the clinical condition was also considered in determining the bacteriological diagnosis. It was also freely acknowledged that the isolation of a potentially pathogenic organism from the nasopharynx was only presumptive evidence that this organism was the causative agent of the respiratory infection.

The pneumococcus was thought to be an infecting agent in 37 per cent of cases, hemolytic *Staphylococcus aureus* in 12 per cent, *Hemophilus influenzae* in 8 per cent, and beta hemolytic streptococcus in 6 per cent. In 37 per cent of cases no potentially pathogenic organism was isolated.

Pneumonia, confirmed radiologically in each case, was the commonest anatomical diagnosis, occurring in 39 per cent of cases. Ten cases of pneumonia occurred in the chlortetracycline group, eight cases in the tetracycline group, and seven cases in each of the three remaining groups. The bacteriology between the various groups was similar with the exception of the chlortetracycline group in which the highest number of infections without associated pathogenic organisms was recorded. The small differences in the incidence and bacteriology of bronchitis, tonsillitis, otitis media, and nasopharyngitis were not considered to be significant.

From the foregoing evidence based on physical characteristics of the patients, clinical diagnosis, and bacteriology, it was concluded that the five therapeutic groups were closely similar in their constitution.

Clinical Response to Treatment.—Despite repeated and careful clinical and laboratory examination of the infants during the course of their illness, it was difficult to establish objective criteria with regard to success or failure of the treatment. It was decided to use only three end points of clinical response, each of which would be absolutely clear cut, and recorded with certainty for each patient. The criteria used were as follows (Table III):

(1) *Failure to Respond to the Therapeutic Agent.*—The decision to discontinue the allotted treatment was made by the physician in charge, not necessarily one of the investigators, after full appraisal of the case. The decision was influenced in some cases by a natural reluctance to continue treating a desperately ill child with oral antibiotics. Pyrexia persisting after forty-eight hours of treatment and the presence of bacteria resistant to the drug in use were the most common reasons for discontinuing treatment. There were two failures in the sulfa group, three in the sulfa plus penicillin group, four in each of the chlortetracycline and tetracycline groups, and five in the oxytetracycline group. These eighteen failures were further considered according to anatomical and bacteriological diagnosis (Table IV). Eleven out of the eighteen failures occurred in cases with pneumonia, four in cases of otitis media, two in cases of bronchitis, and one in a case of tonsillitis. In six out of the eighteen failures no pathogenic

organisms were isolated; in five, hemolytic *Staph. aureus;* in four, pneumococcus; in two, *H. influenzae;* and in 1, beta hemolytic streptococci. There were no failures from treatment with sulfa or sulfa plus penicillin in the pneumococcal infections. The one failure recorded from the use of sulfa admission until the first of two successive readings of 99.0° F. The mean temperature response of 38.7 hours in the sulfa group was considerably but not significantly lower than in the other groups. The average temperature response for all groups was 47 hours.

TABLE III. THE NUMBER OF FAILURES, THE TEMPERATURE RESPONSE IN HOURS FROM ADMISSION, AND THE DURATION OF HOSPITALIZATION IN DAYS FOR EACH THERAPEUTIC GROUP

		SULFA	SULFA AND PENICILLIN	CHLORTETRACYCLINE	OXYTETRACYCLINE	TETRACYCLINE
Cure		18	17	16	15	16
Failure		2	3	4	5	4
Temperature response (hr.)	Mean	38.7	50.1	44.6	52.4	48.0
	Range	6-114	12-96	6-102	6-102	12-126
	S. D.	28.39	30.48	51.16	26.68	35.21
Hospitalization (da.)	Mean	6.9	5.6	6.7	7.1	6.8
	Range	4-13	3-10	3-12	3-15	2-14
	S. D.	2.68	2.35	3.10	3.39	3.01

TABLE IV. ANALYSIS OF EIGHTEEN FAILURES

	PNEUMOCOCCUS	STAPH. AUREUS	BETA HEMOLYTIC STREPTOCOCCUS	H. INFLUENZAE	OTHERS
Tonsillitis					1 Sulfa
Otitis media	1 Chlortetracycline	1 Sulfa 1 Oxytetracycline			1 Oxytetracycline
Bronchitis	1 Oxytetracycline			1 Sulfa + penicillin	
Pneumonia	1 Oxytetracycline 1 Tetracycline	2 Chlortetracycline 1 Tetracycline	1 Sulfa + penicillin	1 Sulfa + penicillin	1 Chlortetracycline 1 Oxytetracycline 2 Tetracycline

plus penicillin in the treatment of beta hemolytic streptococcus pneumonia arose in an infant with a large empyema, from which the organism was cultured. This patient was responding slowly to oral therapy and on the seventh day this was discontinued in favor of intramuscular therapy with large doses of penicillin.

(2) *Temperature Response* (Failures Excluded).—This was measured at 6-hour intervals from the time of

(3) *Duration of Hospitalization in Successful Cases.*—Throughout the periods of study there was a continual demand for hospital beds, so that all patients were discharged as quickly as possible. In many cases the day of discharge coincided with the day on which therapy was discontinued. In only one case was discharge delayed for socioeconomic reasons, and in this case the earliest date on which discharge could have been effected was

calculated from the clinical data. The lowest average duration of hospitalization was 5.6 days, occurring in the sulfa plus penicillin groups, and the highest, 7.1 days in the oxytetracycline group, but the difference between these levels is not significant. The average duration of hospitalization was 6.6 days for all groups.

TOXIC EFFECTS

Certain mild toxic effects were seen in four out of the five therapeutic groups (Table V). In no case were these of sufficient severity to warrant a change of therapy. Diarrhea was recorded as being present if the infant passed two or more watery stools in any one day while on treatment. There were no cases of diarrhea in the sulfa or sulfa plus penicillin groups. Five cases of diarrhea occurred in each of the chlortetracycline and oxytetracycline groups and eight cases in the tetracycline group. Vomiting was recorded as being present if the infant vomited on two or more occasions in any one day while on treatment. There were no cases of vomiting in the sulfa or sulfa plus penicillin groups. One case of vomiting occurred in each of the chlortetracycline and tetracycline groups and four cases in the oxytetracycline group. Transient morbilliform rashes were noted in three cases in each of the chlortetracycline and tetracycline groups and in two cases of the oxytetracycline group. One patient in the sulfa group developed a transient microscopic hematuria.

TABLE V. THE INCIDENCE OF TOXIC EFFECTS

	DIARRHEA	VOMITING	SKIN	HEMATURIA
Sulfa	0	0	0	1
Sulfa + penicillin	0	0	0	0
Chlortetracycline	5	1	3	0
Oxytetracycline	5	4	2	0
Tetracycline	8	1	3	0

FURTHER CONSIDERATION OF BACTERIOLOGY

It was possible by daily repetition of the nasopharyngeal swabs to study the effects of the therapeutic agents on the bacterial flora. In Fig. 1 the percentage of positive nasopharyngeal swabs for the potentially pathogenic organisms including pneumococcus, hemolytic *Staph. aureus*, beta hemolytic streptococcus, and *H. influenzae* have been plotted against the days in hospital. Patients treated with sulfa and sulfa plus penicillin have been combined to form one group, and those treated with the three tetracycline antibiotics combined in the other group. On the day of admission 78 per cent of the infants in the first group had cultures positive for one of the four organisms, and this had fallen to 18 per cent on the third hospital day, and 9 per cent on the fourth hospital day. For the second group the corresponding figures were 64 per cent on the first day, 36 per cent on the third day, and 29 per cent on the fourth day. After the fourth day the two groups approximated more closely. The difference between the two groups was due to the fact that sulfa and sulfa plus penicillin were more effective than the other antibiotics in clearing the nasopharynx of pneumococci.

Antibiotic sensitivity tests were carried out on the staphylococci isolated from the twelve cases in which this was thought to be the causative organism. In three cases the staphylococcus was sensitive to penicillin; in six cases it was sensitive to chlortetracycline, oxytetracycline, and tetracycline; in eleven cases it was sensitive to chlor-

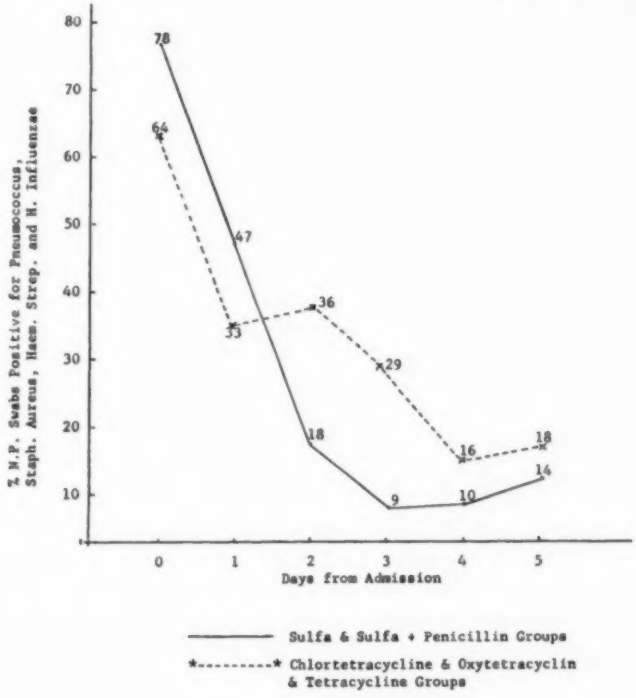

Fig. 1.

amphenicol; and in all cases it was sensitive to erythromycin. In two cases of staphylococcal pneumonia in which treatment was commenced with chlortetracycline, the results of bacteriological sensitivity examinations were considered to be lifesaving, in that they drew attention to errors in therapy which were promptly rectified with good results.

DISCUSSION

The first problem to which an answer was sought from the results of this investigation was the usefulness of bacteriological investigation as an aid to diagnosis and treatment of acute respiratory disease. Potentially pathogenic organisms were isolated from the nasopharynx in 63 per cent of the cases, and in the remaining 37 per cent no such organisms were found.

The pneumococcus was most frequently isolated, occurring in 37 per cent of all cases. Typing of pneumococci was not carried out. Evidence from two sources suggested that respiratory infections associated with this organism responded better to

treatment with sulfa or sulfa plus penicillin than to treatment with one of the tetracycline group of drugs.

(1) In cases with pneumococcal infection there were no failures in the sulfa or sulfa plus penicillin groups.

(2) Examination of daily nasopharyngeal swabs showed that pneumococci disappeared more rapidly and more completely in infants receiving sulfa or sulfa plus penicillin.

It is possible that these differences would have been eliminated or even reversed if the tetracycline group of drugs had been used in a dosage greater than 10 mg. per pound per day.

The chief advantage of bacteriological investigation in this study lay in the detection of infections associated with *Staph. aureus* (12 per cent) and *H. influenzae* (8 per cent). The former produced the most virulent infections which were least likely to respond to sulfa, penicillin, or the tetracycline group of drugs. All the staphylococcal cultures were sensitive to erythromycin, and this was the drug of choice where the infection was resistant to one of the other therapeutic agents. Two patients with *H. influenzae* infection resistant to treatment with sulfa plus penicillin responded rapidly to treatment with streptomycin.

No attempt was made to isolate viruses in the present study, and even where detailed bacteriological and virological studies have been carried out it has been no easy matter to determine whether the etiology was bacterial or viral. Thus Crofton and associates,[1] in a study of 110 adults admitted to hospital with pneumonia, found that a specific etiological agent was demonstrated by laboratory investigation in only fifty-eight cases. In twenty-six out of the 110 cases there was some evidence of rickettsial or virus infection. In an investigation of eighty adults suffering from acute infections of the chest seen in general practice, Batty Shaw and Fry[2] found that it was possible to demonstrate a specific bacterial etiology in only 17.5 per cent of cases and a viral etiology in 18.8 per cent. There is little evidence that viral studies to date have been of much value in the treatment of acute respiratory disease, chiefly because of the long delay in obtaining results from the laboratory. Even if speedier methods of viral diagnosis were evolved, it might well be that the bacterial partner of a combined bacterial viral infection would be of greater importance, as has been seen in the appearance of virulent cases of staphylococcal pneumonia during epidemics of influenza A virus.[3, 4]

The second problem to which an answer was sought, was the relative efficacy of a variety of therapeutic agents in the treatment of acute respiratory infections. No significant difference in clinical response could be demonstrated between a sulfonamide suspension, a mixture of sulfa and penicillin, chlortetracycline, oxytetracycline, and tetracycline. Indeed the increased incidence of minor toxic effects, the poorer response of pneumococcal infections, and the greater expense of treatment with the tetracycline group of drugs suggested that these should yield first place to sulfonamides or penicillin in the initial treatment of respiratory infections of unknown etiology. It may well be that the dosage of 10 mg. per pound

per day for the tetracycline group of drugs was too small.

The results of this investigation are in agreement with the few reported studies of a similar nature. The report of the antibiotics clinical trials committee of the Medical Research Council in Britain[5] compared the results of therapy with chlortetracycline, chloramphenicol, and penicillin in 267 adult patients suffering from pneumonia. There were no significant differences in response to treatment in the three therapeutic groups, although the incidence of toxic effects from chlortetracycline and chloramphenicol was considerably higher than with penicillin. Eadie and associates[6] compared chlortetracycline with penicillin administered orally in seventy-nine adult patients with pneumonia and found no differences in the efficacy of the two drugs. Fisher and Whitfield[7] compared two groups of twenty-five infants suffering from pneumonia. One group received oxytetracycline in a dose of 20 mg. per pound per day and the other received sulfa orally and penicillin intramuscularly. The response to treatment was similar in each group. Hardy and Traisman[8] studied a large group of inpatient and outpatient children suffering from respiratory infections. Over 50 per cent of the children observed were untreated controls, the remainder being treated with Gantrisin, penicillin, or broad-spectrum antibiotics. A complication rate of 15 per cent was present in the treated and untreated groups, but complications developed sooner in the treated groups and could be classified as predominantly viral. There was no evidence that treatment with chemotherapeutic or antibiotic agents shortened the recovery time of the patients studied.

In vitro studies[9] and study of experimental infections in animals[10] have failed to reveal any striking differences between chlortetracycline, oxytetracycline, and tetracycline. It was therefore not surprising that the present study revealed no differences in clinical response between the three groups treated with these drugs. Mild toxic effects were more frequently seen with tetracycline than with chlortetracycline or oxytetracycline.

In conclusion it was felt that this study had provided some information which was of value in considering the problems of respiratory infections in young children. Nasopharyngeal swabs were of definite value in diagnosis and in the selection of therapy. While awaiting the results of bacteriological investigation it is perfectly justifiable, where active treatment is indicated, to commence with sulfa or penicillin or both. Defervescence of fever as a sign of response to treatment should not be expected for a period of thirty-six to forty-eight hours no matter what drug is being used. At the end of thirty-six hours the results of bacteriological investigations should be available. If these throw no light on the diagnosis and the temperature remains elevated, it is justifiable to discontinue treatment with sulfa or penicillin and employ one of the broad-spectrum antibiotics. In private practice, and surely the great majority of acute respiratory infections are treated at home, bacteriological control of treatment is more difficult to achieve. But the same principles apply, that treatment where indicated should be instituted with sulfa or penicillin and changed to another antibiotic only in

the presence of progressive clinical deterioration or the persistence of fever beyond a period of thirty-six to forty-eight hours.

SUMMARY

One hundred infants under the age of 3 years and suffering from acute respiratory disease were divided into five equal groups. Each group was treated with one of the following therapeutic agents administered orally:

1. Sulfamethazine 0.1 Gm. per pound per day.
2. Sulfamethazine 0.1 Gm. per pound per day plus 30,000 I.V. dipenicillin G dibenzylethylene diamine per pound per day.
3. Chlortetracycline 10 mg. per pound per day.
4. Oxytetracycline 10 mg. per pound per day.
5. Tetracycline 10 mg. per pound per day.

Comparison of failure rate, temperature response, and duration of hospitalization did not reveal any significant differences between the five groups. Minor toxic effects such as diarrhea, vomiting, and skin rashes were more frequently observed in groups 3, 4, and 5.

Bacteriological studies suggested that sulfamethazine and sulfamethazine plus penicillin were more effective than broad-spectrum antibiotics against pneumococcal infections.

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CONGENITAL DEFECTS IN INFANTS FOLLOWING MUMPS DURING PREGNANCY

A Review of the Literature and a Report of Chorioretinitis Due to Fetal Infection

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WHEREAS it is generally accepted that the rubella infection in the mother during the first trimester of pregnancy can cause fetal death or congenital malformation, the relation of maternal mumps to fetal damage is less certain.

In Warkany's[1] comprehensive review of the etiology of congenital malformation, reference is made to articles refuting the harmful action on the fetus of viruses other than that of rubella. Nevertheless, he expressed the sage prediction that "the future may provide many surprises in this field."

The following case report is one of congenital chorioretinitis in which the apparent etiology was fetal mumps virus infection.

CASE REPORT

P. K., a white girl, was first seen at St. Louis Children's Hospital at 6 months of age because "she doesn't see like she should."

The history is as follows. The mother, a 28-year-old nurse, was gravid ii, para i. The previous pregnancy was normal. Her blood type was Rh positive and the blood Kahn was negative. The date of the last menstrual period was March 11, 1954, and the expected date of confinement, December 18. Early pregnancy was complicated by hyperemesis. On July 10 she developed bilateral parotid swelling (mumps). There was a low-grade fever and the swelling remained eight to ten days. Eighteen days previously she had been exposed to mumps from the physician for whom she worked.

On December 18 she delivered spontaneously. The infant weighed 6 pounds 12 ounces. There was difficulty in resuscitation and the baby was placed in an incubator with oxygen for several hours. At 3 or 4 hours of age her color and cry were normal. Breast feeding was begun at 24 hours and she nursed well. There was no unusual neonatal jaundice.

Since birth the mother noticed that the baby's eyes "crossed in." There was purposeless eye movement and an "inability to focus." She mentioned this to her physician prior to discharge from the hospital and was reassured. The child's mental development appeared normal—she smiled at 6 weeks, could roll completely over at 4 months, and in the previous few weeks had been holding on to objects with her hands. Her hearing appeared normal.

The only illness since birth was a mild case of chicken pox at 3 months of age. She was exposed to her sister. "She was not sick. There was very little fever, no drowsiness or irritability." The mother reiterates the "eye signs very definitely preceded the chicken pox." The patient has one female sibling, aged 6 years, alive and

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well. The paternal grandmother had diabetes. The family history was otherwise nonrelevant (no congenital defects).

Physical examination revealed a normally responsive, well-nourished and well-developed infant. The head was normal in shape. The occipital frontal circumference measured 43.2 cm., chest 43 cm. The eyes showed a searching type of nystagmus. The lids, lacrimal apparatus, conjunctiva, corneas and scleras were normal. There was an exotropia of 15 degrees, Hirschberg evaluation, with no tendency to fix with either eye. The pupils reacted sluggishly to light. The tension of each eye appeared normal by palpation. The media were clear. Both discs were markedly atrophic. The left optic disc was about one-half the size of that on the right. Atrophic scars with peripheral pigmentation were seen in the region of the maculas of both eyes and an additional area of atrophy was present between the disc and macula of the left eye. There was a peculiar mottling of the entire fundus bilaterally. There was a grade I nonpersistent systolic precordial murmur. Apart from the abnormal eye findings the neurological examination was physiological. There was a tendency for the right foot to assume an equinovarus position.

The clinical impression was chorioretinitis due to congenital toxoplasmosis. Skull x-rays were normal. Maternal serum gave a positive methylene blue dye test for toxoplasma antibodies in a titer of only 1:16 and serum from the child was negative. These results exclude congenital toxoplasmosis.

At age 12 months she was walking with assistance and saying single words. She weighed 19 pounds 13 ounces and was 27¾ inches tall. The occipital frontal circumference measured 46.5 cm. and the chest 46 cm. Apart from the eye findings the general physical and neurological examinations at this time were entirely normal.

When last seen on June 6, 1956, at age 18 months, she had been walking without support for several months and was putting words together. There was an interval history of frequent upper respiratory infections with low-grade fever. Repeat skull films at this time revealed a huge adenoid mass, and adenoidectomy was recommended. On this date serum was drawn from the child for mumps complement fixing antibody and a mumps skin test was made. No complement fixing antibodies were detected. Within twenty-four hours of skin testing there was intense erythema 20 mm. in diameter, in the center of which was an area of induration 7 mm. wide and 1 mm. thick. These findings were unchanged at forty-two hours, and she developed a temperature of 101.6° F. rectally. No control material was supplied with the skin test antigen. To exclude the possibility of egg sensitivity, 0.1 c.c. of egg white antigen containing 100 phosphotungstic nitrogen units per cubic centimeter was injected intradermally. There was neither an immediate nor delayed reaction. A Vollmer patch test was negative.

REVIEW OF THE LITERATURE

A review of the reported noxious results of maternal mumps during gestation reveals the following.

Mumps and Abortion.—In 1948 Greenberg[2] mentioned a case in which "epidemic" parotitis occurred three days after spontaneous abortion at 3½ months' gestation.

Fox and associates[3] reported twenty-three cases of mumps during pregnancy, one of which ended in spontaneous abortion at 2 months.

In their review of infectious diseases during pregnancy Grönvall and Selander[4] found one case of maternal mumps with abortion in the second month of pregnancy.

Schwartz[5] describes a case of abortion during convalescence from mumps in the fourth month of pregnancy. Of significance in evaluating this relationship is the statement that this multipara "had considerable difficulty in conceiving."

In 1953 Ylinen and Järvinen[6] reviewed the subject of parotitis during pregnancy. This report included three cases of their own of abortion occurring after mumps in the third month of pregnancy. They also reported a premature delivery nine days after mumps infection in the seventh month of pregnancy.

Bowers[7] reported a para ii who developed bilateral parotitis in the fifth week of pregnancy; two days later she expelled a macerated fetus. Another case, a para iii, aborted after parotitis in the tenth week of pregnancy.

Mumps and Stillbirth.—In 1931 Moore[8] reported the birth of a stillborn infant of 8 months' gestation. The mother had had mumps one month previously. During this illness she was comatose, with high temperature, and "her heart behaved badly." Considering that this woman had severe heart disease (mitral stenosis) and almost died during a previous pregnancy, any association may be questioned.

In Swan's[9] analysis of the histories of 760 cases of stillbirth, there appears to be five cases in which the mothers had mumps during pregnancy. In three instances, two of mumps infection alone and one of mumps plus whooping cough, no further details were given. In Case 10 there was mumps in the first month and rubella in the third month of pregnancy. Twin delivery occurred fifteen days before expected confinement. Since one twin was alive and normal, the relationship of the infectious diseases during pregnancy to the delivery of the stillborn twin is not obvious. In Case 13 the mother had mumps and rubella in the fifth month of pregnancy. The attending physician attributed the stillbirth to premature separation of the placenta.

Mumps and Congenital Abnormalities.—In 1943 Swan and associates[10] reported an infant born with bilateral corneal opacities without ciliary injection. The mother had had mumps at 3½ to 4 months' gestation. On a follow-up examination at age 20 months the left cornea had cleared entirely and the right was improved. It was their opinion at this time that "in the absence of similar cases, however, the association between mumps during pregnancy and corneal opacity must remain doubtful."

Later Swan and Tostevin[11] reported an infant born with an imperforate anus. The mother had had mumps in the first month of pregnancy. We did not consider the case of "slight capillary naevus of the right upper eyelid" (mumps first month of pregnancy) or Case 127, with a head circumference "slightly below normal" (mumps in seventh month of pregnancy) as particularly relevant to the maternal mumps infection.

Grönvall and Selander[4] listed five cases of congenital defects in infants born of mothers who had mumps during pregnancy. One was a case of spina bifida occulta (mumps in the first month of pregnancy). In two cases, a urogenital deformity and organic nerve disease (Little type), both mothers had mumps in the fifth month of pregnancy. There was one mongoloid birth following mumps in the

sixth month and a congenital cardiac anomaly associated with mumps in the eighth month of pregnancy. The authors questioned the relationship of the latter two anomalies to mumps so late in pregnancy. It is not clear why they considered the case of organic nerve disease to be more significant in relation to the maternal infection than the urogenital system anomaly, since both occurred during the same month of pregnancy (fifth).

Greenberg and Beilly[12] described an infant born with a congenital abnormality of the right ear. It appears that the mother acquired mumps on the eighth day after conception.

Dumont[13] considered a case of hypospadius to be related to maternal mumps in the third month of pregnancy.

In 1952 Bertoye and colleagues[14] reported congenital cardiopathy in dizygotic twins due to maternal mumps.

That same year Di Ferdinando[15] described abnormalities seen in two infants whose mothers had rubella and mumps in the first trimester of pregnancy.

Grassi[16] describes a case of fetal meningoencephalitis associated with maternal mumps in the fourth month of pregnancy. The delivery was a twin birth. One infant was stillborn. His head consisted of a water-filled cyst. The living infant soon showed mental retardation, spasticity, retinal anomalies, and hydrocephalus.

The above three articles were not available to us in their original form for review.

Ylinen and Järvinen[6] reviewed the literature on this subject and reported two cases of their own—one a "monster" with many congenital defects and the other a case of intestinal atresia. In both instances mumps occurred in the first trimester of pregnancy. Considering the suspicion of maternal toxoplasmosis in Case 7 (parotitis in fourth month of pregnancy), the relationship of the mongoloid infant to the parotitis is not clear.

DISCUSSION

Unfortunately none of the above surviving infants had complement fixation for mumps antibody or mumps skin tests performed.

It has been shown that mumps complement fixing antibodies readily cross the placenta. Levels for such antibodies are essentially identical in maternal and cord blood.[17, 18] Characteristically these passively transferred antibodies are short-lived. Florman and Karelitz[19] determined the duration of survival of these transplacental antibodies (complement fixing and agglutination inhibiting) to average 53 and 45 days, respectively.

Complement fixing antibody titers in adults comparable to neonatal levels are associated with positive skin reactions to mumps virus antigen. Mumps skin hypersensitivity has not been determined in the newborn infant. Fourteen newborn infants (age range from less than 12 hours to 6 days) were skin tested with mumps virus antigen and control material (Lederle). Whereas all of the mothers gave positive reactions (15 mm. erythema or more) none of their infants did.[20]

Although complement fixation and skin allergy do not appear to be related either as to time of appearance or duration of positivity,[21] both imply immunity to mumps as correlated with past history and resistance to subsequent exposure. Complement fixation

is found within three weeks of onset of mumps, whereas dermal hypersensitivity appears during late convalescence and persists longer. For this reason Enders[22] prefers the mumps skin test as an expression of past infection. Several authors[23, 24] have noted that children react less well to skin antigen than adults even with comparable complement fixing antibody levels. However, Enders and associates[23] wonder if this merely means a recently acquired infection with a relatively high complement fixing antibody titer and as yet minimal skin allergy.

In our case the diagnosis of mumps in the mother is unquestioned. Complement fixation on the infant was done at a time (eighteen months after birth and twenty-three months after presumed fetal infection) when passively transferred antibody would definitely be gone[18, 19] and acquired antibody possibly so.[21]

The possibility of subclinical mumps infection after birth is remote. There was no postnatal exposure to mumps and with more recent infection one would expect a detectable complement fixing antibody titer and less skin sensitivity. The findings in our case of negative complement fixation and a strongly positive skin test are in agreement with Enders'[22] feeling that "allergy to the virus can be demonstrated in certain individuals in whom the antibody has sunk to a subthreshold level, and accordingly that the skin test in most instances should prove to be an even more accurate index of past infection than the determination of antibody."

Though fetal mumps virus infection seems certain in our patient, its relation to the chorioretinitis is admittedly not proved. The association is, however, highly probable.

The commonest known cause of congenital chorioretinitis is Toxoplasma infection. However, in Sabin's[25] early series of forty-three cases of congenital chorioretinitis, only about one-half were of this etiology, and he expressed the feeling that nontoxoplasmic chorioretinitis was probably a far more common entity. In July, 1956, Feldman and Miller[26] found this incidence unchanged.

Noninfectious causes of congenital chorioretinopathy are developmental defects, maternal x-ray irradiation, fetal and neonatal trauma, and retrolental fibroplasia.

Chorioretinitis has been attributed to various infections—syphilis, tuberculosis, influenza, and even to nematode infestation. Such an association is seldom confirmed in congenital chorioretinitis, the majority being of either unproved etiology or examples of congenital toxoplasmosis.

Recently we have seen a patient with proved congenital salivary gland virus disease, who exhibited dense paraventricular calcification. There was no chorioretinitis. This case exemplifies still another cause for cerebral calcification, and the possibility of ocular lesions of this etiology should not be overlooked.

Considering that the majority of cases of congenital chorioretinitis are of undiscovered etiology and in view of the ubiquity of mumps infection, we feel that cases of nontoxoplasmic origin should be investigated from this point of view. Careful inquiry into the history of pregnancy and the judicious use of complement fixation and skin testing may help elucidate specific

etiology. However, a negative maternal history during gestation does not exclude mumps. Enders and associates have proved the high incidence of inapparent or subclinical infection in the general population. About one-half of those who deny ever having mumps have positive serology for mumps complement fixing antibodies.[17] This line of thought is in agreement with Dumont's[27] impression that subclinical infection in the mother can be of etiological significance in congenital abnormalities. This would particularly be true in cases of mumps infection since it is estimated that about one-third of all such infections are subclinical.[17] Furthermore, considering the seeming risk of such infection in pregnancy, particularly in the early months where exposure is known, the use of mumps vaccine should seriously be considered.

CONCLUSION

Mumps virus infection in early pregnancy can affect the fetus adversely. A case of congenital chorioretinitis has been attributed to such infection. It is recommended that in cases of congenital defects following maternal mumps, complement fixation and skin testing be performed on these infants (after age 2 months) to establish this causal relationship.

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PNEUMOENCEPHALOGRAPHY IN TUBERCULOUS MENINGITIS

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TUBERCULOUS meningitis is now a curable disease. This became possible for the first time in 1947, with the advent of streptomycin. From 1947 to 1952 the survival rate in the Children's Medical Service of the Bellevue Hospital[1] was maintained at over 60 per cent using streptomycin and Promizole. After 1952, when isoniazid became available, the number of survivors increased everywhere. At the present time the survival rate is reported to be from 60 to 95 per cent,[2-4] depending upon the stage and duration of the disease at the onset of therapy.

In order to evaluate the results of therapy of tuberculous meningitis, it is necessary to search for neurological sequelae by means of neurological examinations, psychometric studies, audiometry, and pneumoencephalography. This communication will concern itself with the use of pneumoencephalography in determining diagnosis and prognosis.

Neurological sequelae in tuberculous meningitis may be produced in various ways. They may be due to cerebral thrombosis followed by necrosis and not infrequently by intracranial calcifications. These calcifications may be associated with contralateral hemiparesis. On the other hand, sequelae may be related to disturbed cerebrospinal fluid circulation. Most commonly there is interference with the circulation of cerebrospinal fluid at the base of the brain[5] and the fluid does not reach the subarachnoid space at the convexity of the brain where most of it is absorbed. A communicating type of hydrocephalus results. Less frequently hydrocephalus in tuberculous meningitis is due to obstruction in the foramina of Magendie, Luschka, or Monro, or in the aqueduct of Sylvius. Hydrocephalus may produce symptoms and signs or may be present in an apparently normal child. It may occur during the acute phase of the disease or may develop insidiously while the patient is apparently improving. It may persist for several years or it may disappear while the tuberculous lesions heal.

In 1947 Lincoln[6] presented autopsy evidence that the occurrence of hydrocephalus bore a direct relation to the severity and to the duration of the disease. The brains of nine out of ten children who died of tuberculous meningitis less than three weeks after

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onset of the disease showed hydrocephalus, usually of slight degree, whereas fourteen of twenty-two autopsies of children dying after more prolonged illness revealed hydrocephalus which was in most cases of greater severity. The implication that hydrocephalus occurs more frequently in cases of longer duration is of importance not only in early diagnosis and treatment of the disease, but also in the management of the survivors. Therefore, a procedure like pneumoencephalography should be of great value in evaluating the course and prognosis of patients with tuberculous meningitis. This has been stressed in recent communications on the results of pneumoencephalography in tuberculous meningitis[5,7] which have appeared in the European literature.

Pneumoencephalography in tuberculous meningitis was first performed on twenty patients by Eckstein[8] in 1927. Varying degrees of hydrocephalus were found; this information supported the concept that hydrocephalus was invariably present in tuberculous meningitis. Specific therapy renewed interest in the disease and in 1948 Murano[9] extensively reviewed the literature and studied nineteen patients, finding abnormalities in seventeen. Other investigations followed, but the first extensive study was done by Lorber in 1951, when he reported the results of one hundred tests performed in fifty-eight unselected cases. Abnormalities were discovered in thirty-six cases: of these, thirty-four had hydrocephalus. A block at the tentorial opening or basal cisterns was present in thirty cases and a block at the Sylvian aqueduct or the foramina of the fourth ventricle was noted in five cases. There was a close correlation between the encephalographic appearance and the prognosis. In none of Lorber's cases was there evidence of relapse of the disease due to the procedure. He reported one death twenty-four hours following ventriculography in an infant with extreme hydrocephalus. More recently Durand and de Maestri[10] have stressed the use of cisternography in studying the patterns of obstructions in the disease. In the American literature Atkins and Cummings[11] and Foltz and Sheehy[12] have pointed out the value of ventriculograms and pneumoencephalograms in the diagnosis and treatment of spinal and basal block.

MATERIAL AND METHODS

The plan of this investigation was to study the pneumoencephalographic appearance in a group of children who had recovered or were recovering from tuberculous meningitis and relate the findings to the status of the child physically and mentally. In addition, a group of cases was studied early in the course of the disease and another small group during the later phase of treatment.

These studies were performed on children with tuberculous meningitis treated in the Children's Medical Service of Bellevue Hospital.

The lumbar route was utilized for the injection of air in most of the cases. Air replacement was performed in the erect position and films taken at a 6-foot distance, in the upright posteroanterior and lateral position after 20 c.c. of air had been injected. Further replacement was performed as necessary and films taken in the anteroposterior, posteroanterior, and right and left lateral projections with the patient in the horizontal position.

When the films were reviewed the diagonal width of the lateral ventricles was used as the basis for measurement.[13]

All living patients have been followed three years or more after completion of therapy.

RESULTS

Thirty-eight air studies were performed upon twenty-seven patients. The data on these patients and the results of the studies are summarized in Tables I, II, and III according to the abnormalities observed.

Fig. 1.—Pneumoencephalogram of a 3-year-old female child who was studied twice during the course of therapy for tuberculous meningitis and once three months after completion of therapy. This patient is deaf, and has petit mal seizures. All three air studies showed moderate degree of hydrocephalus and absence of air in the subarachnoid space.

Table I shows that ten patients had hydrocephalus of various degrees of severity. The following patients illustrate this group:

Patient 1, L. K. (Fig. 1) was studied with three separate pneumoencephalograms, two during the course of treatment and one three months after the completion of therapy. This patient is deaf, has evidence of brain damage and a convulsive disorder. The air studies showed a moderate hydrocephalus and absent subarachnoid air in the sulci over the surface of the brain. There was no change on measurement and no clinical evidence of progression two years seven months later upon repeated pneumoencephalography.

Another patient, No. 5, S. S. (Fig. 2) had severe hydrocephalus which continued to progress even after the cerebrospinal fluid returned to normal.

Fig. 2.—Pneumoencephalogram of a 2-year-old female child who had apparently recovered from tuberculous meningitis but was physically and mentally retarded. This upright lateral view shows marked hydrocephalus with thinning of the cerebral cortex and block at the rostral end of the cisterna interpeduncularis. There is no subarachnoid air.

She died of a purulent meningitis following several attempts at arachnoid-peritoneal shunts.

Patient 7 had hydrocephalus due to block at the cisterna interpeduncularis and at T_{11} and T_{12} (Fig. 3). This patient was treated with an enzyme, pancreatic dornase, and cortisone, but did not respond and died during the second month of therapy.

TABLE I. PATIENTS WITH HYDROCEPHALUS*

CASE NO.	AGE AT ONSET OF MENINGITIS	DURATION OF SYMPTOMS BEFORE DIAGNOSIS	STAGE AT DIAGNOSIS	PEG TIME AFTER ONSET	PRESENCE OF SUBARACHNOID AIR OVER THE CONVEXITY	RESULT OF PEG	GENERAL CONDITION ON LAST OBSERVATION	NEUROLOGICAL SEQUELAE	INTELLIGENCE	DURATION OF FOLLOW-UP AFTER ONSET
1	24 mo.	4 wk.	Early	2 mo. 4 mo. 9 mo.	No No No	Moderate hydrocephalus No change in size of ventricles	Fair	Deaf; petit mal; generalized convulsions	Impossible to classify, probably average potential; brain injured	60 mo.
2	27 mo.	4 wk.	Moderately advanced	7 da.	No	Moderate hydrocephalus	Fair	Deaf; right hemiplegia improving	IQ = 54	50 mo.
3	6 mo.	9 da.	Late	16 da.	No	Ventriculogram marked hydrocephalus	Died			2 mo., died
4	9 mo.	Diagnosed by routine tap because of miliary tuberculosis	Early	24 mo.	No	Marked hydrocephalus	Died 3 da. after test		Probably retarded	24 mo., died
5	15 mo.	3 wk.	Early	10 mo.	No	Marked hydrocephalus; block in cisterna interpeduncularis	Died of purulent meningitis following attempted shunt	Progressive and physical mental retardation		21 mo., died

*In this and all the other tables time intervals were calculated before or after onset of therapy for tuberculous meningitis. All tests were pneumoencephalograms performed through the lumbar route except when otherwise stated. The stages of disease were figured at the onset of therapy: early means—absent neurological signs; moderately advanced—neurological signs present but patient was conscious; late—unconscious or decerebrate.

6	26 mo.	11 da.	Late	7 da.	No	Marked hydrocephalus; block at cisterna interpeduncularis and pontis	Died	Decerebrate		2 mo.
7	4 yr.	9 da.	Moderately advanced	2 wk.	No	Ventricles did not fill; block at T_{11} and T_{12}	Died	Decerebrate		2 mo., died
8	16 mo.	3 wk.	Late	3 mo.	No	Marked hydrocephalus	Poor	Decerebrate	Imbecile	47 mo.
				5 mo.	No	Marked hydrocephalus				
9	17 mo.	12 da.	Moderately advanced	2 wk.	No	Only slight ventricular filling		Blindness and deafness reversed after enzyme therapy	Apparently normal	Block successfully treated with pancreatic dornase by intrathecal and intravenous routes
				4 wk.	No	Ventriculogram: marked obstruction at foramina of Lushka and Magendie				
				5 wk.	No	Hydrocephalus persists but filling of ventricles from lumbar region was possible				
				3 mo.	No	Ventriculogram: no change	Good			41 mo.
10	14 mo.	1 wk.	Moderately advanced	4 da.	No	Upper limits of normal	Fair	Right hemiparesis	Probably dull normal	48 mo.
				9 wk.	No	Marked dilatation of left ventricle (lat.)				

TABLE II. PATIENTS WITHOUT FILLING OF VENTRICLES BUT FILLING OF SUBARACHNOID SPACE WITH AIR

CASE NO.	AGE AT ONSET OF MENINGITIS	DURATION OF SYMPTOMS BEFORE DIAGNOSIS	STAGE AT DIAGNOSIS	PEG TIME AFTER ONSET	PRESENCE OF SUBARACHNOID AIR OVER THE CONVEXITY	RESULT OF PEG	GENERAL CONDITION ON LAST OBSERVATION	NEUROLOGICAL SEQUELAE	INTELLIGENCE	DURATION OF FOLLOW-UP AFTER ONSET
1	3½ mo.	4 wk.	Early	11 mo.	Yes	Air present in subarachnoid space and basal cisterns but not in ventricles	Good	Deaf	IQ = 83	61 mo.
2	16 mo.	3 wk.	Moderately advanced	36 mo. 38 mo. 39 mo.	Yes	Air present in subarachnoid space and basal cisterns but not in ventricles	Good	Deaf, epilepsy	IQ = 99	89 mo.

Patient 9 is of interest because he had obstruction at the level of the foramina of Luschka and Magendie; this was suspected because of slight filling of the ventricles when air was injected throught the lumbar route (Fig. 4). The site of the block was later confirmed by ventriculography (Fig. 5). This patient was successfully treated with pancreatic dornase

Fig. 3.—Air myelogram of a 4-year-old male child on the second week of therapy for far-advanced tuberculous meningitis. This air myelogram shows obstruction to the passage of air, injected in the lumbar region, beyond T_{11} and T_{12}.

Fig. 4.

Fig. 5.

Fig. 4.—Pneumoencephalogram of a 17-month-old infant during second week of therapy for advanced tuberculous meningitis. There is only slight filling of the ventricles, but there is subarachnoid air.

Fig. 5.—Ventriculogram of same patient as Fig. 4 shows marked dilatation of the ventricles and obstruction to the passage of air beyond the foramina of Luschka and Magendie.

by intravenous and intrathecal routes with resolution of the block, as demonstrated by subsequent air studies.

Patient 10 had a right hemiparesis at the time therapy was started for marked dilatation of the left lateral ventricle (Fig. 7). The absence of subarachnoid air in the first study suggested obstruction of the cerebrospinal fluid circulation.

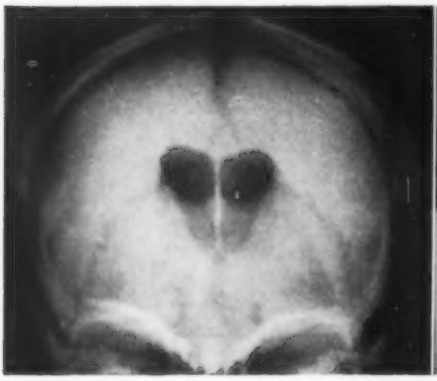

Fig. 6.

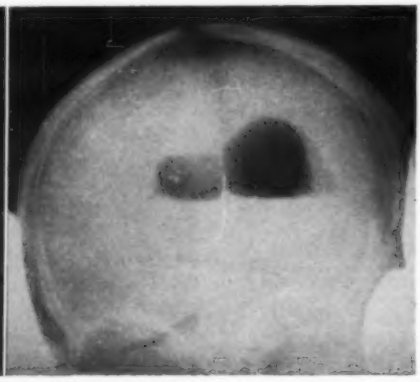

Fig. 7.

Fig. 6.—Pneumoencephalogram of a 14-month-old female infant on her fourth day of therapy for tuberculous meningitis. The ventricles are normal, but there is no subarachnoid air. The patient has right hemiparesis.

Fig. 7.—Pneumoencephalogram of the same patient as Fig. 5 on the ninth week of therapy for tuberculous meningitis. The left lateral ventricle is markedly dilated. The right hemiparesis persists.

Fig. 8.—Pneumoencephalogram of a 4½-year-old female child who has recovered from tuberculous meningitis and is physically and mentally well except for deafness. Injections of air into the lumbar region on three occasions revealed identical results: absence of air in the ventricle, but abundant subarachnoid air.

tuberculous meningitis. Pneumoencephalography (Fig. 6) on the fourth day of therapy showed normal ventricles. Eight weeks later there was

Table II shows patients without hydrocephalus who had no filling of the ventricles. One of these, F. F. (Fig. 8), had moderately advanced

TABLE III. PATIENTS WITH NORMAL PNEUMOENCEPHALOGRAMS

CASE NO.	AGE AT ONSET OF MENINGITIS	DURATION OF SYMPTOMS BEFORE DIAGNOSIS	STAGE AT DIAGNOSIS	PEG TIME AFTER ONSET	PRESENCE OF SUBARACHNOID AIR OVER THE CONVEXITY	RESULT OF PEG	GENERAL CONDITION ON LAST OBSERVATION	NEUROLOGICAL SEQUELAE	INTELLIGENCE	DURATION OF FOLLOW-UP AFTER ONSET
1	13 mo.	3 wk.	Early	48 mo.	Yes	Normal	Good	Deaf	IQ = 79	99 mo.
2	6 mo.	10 da.	Early	36 mo.	Yes	Normal	Good	Deaf; brain injured	IQ = 78 (probably higher)	73 mo.
3	18 mo.	3 wk.	Early	12 mo.	Yes	Normal	Good	Deaf; arachnoiditis	IQ = 98	64 mo.
4	22 mo.	2 wk.	Early	11 mo.	Yes	Normal	Good	Deaf (left hemiplegia)	IQ = 73	65 mo.
5	2 yr.	2 wk.	Early	4 mo.	Yes	Normal	Good	Ataxia-epilepsy; deaf	Brain injured	63 mo.
6	20 mo.	5 da.	Early	6 mo.	No	Normal	Good	Deaf	Average normal	63 mo.
7	3 yr.	1 wk.	Early	5 mo.	Yes	Normal	Good	Deaf	IQ = 103	61 mo.
8	4 yr.	2 wk.	Moderately advanced	1 mo. 2 mo. 4 mo.	Yes Yes Yes	Ventricles at upper limits of normal	Good	None	IQ = 112	57 mo.
9	13 mo.	7 da.	Early	3 mo.	No	Ventricles at upper limits of normal	Good	Deaf	IQ = 77 (probably higher)	53 mo.
10	2 yr.	2 wk.	Moderately advanced	9 da.	Yes	Normal	Good	Emotionally unstable and brain injured	IQ = 69	52 mo.
11	13 yr.	2 wk.	Moderately advanced	1 mo.	Yes	Normal	Good; healed Tb. spondylitis	Deaf	Probably dull normal	51 mo.
12	30 mo.	2 wk.	Early	2 wk.	Yes	Normal	Good	None	IQ = 97	49 mo.
13	10 yr.	9 da.	Early	6 wk.	Yes	Normal	Good	None	IQ = 91	49 mo.
14	23 mo.	9 da.	Early	5 da.	Yes	Normal	Good	None	IQ = 86 (probably higher)	43 mo.
15	17 mo.	1 mo. (?)	Moderately advanced	11 da.	Yes	Normal	Good	None	Apparently normal	43 mo.

TABLE IV. CORRELATION OF RESULTS OF PNEUMOENCEPHALOGRAPHY WITH NEUROLOGICAL SEQUELAE, MORTALITY, DURATION AND STAGE OF ILLNESS AT ONSET OF THERAPY, PRESENCE OF SUBARACHNOID AIR, AND AGE OF PATIENTS

	MORTALITY			WEEKS OF ILLNESS BEFORE ONSET OF THERAPY			STAGE OF ILLNESS AT ONSET OF THERAPY			FILLING OF SUBARACHNOID SPACE WITH AIR		AGE IN MONTHS		
		Living												
	Dead	Neurological sequelae*	Well	Less than 1 wk.	1 to 2 wk.	More than 2 wk.	Early	Mod. Adv.	Late	Yes	No	Less than 18	18 to 36	More than 36
Patients with hydrocephalus (10)	5	4	1	1	5	4	3	4	3	0	10	6	3	1
Patients without filling of ventricles (2)	0	1	1	0	0	2	1	1	0	2	0	1	0	1
Patients with normal pneumoencephalograms (15)	0	5	10	1	11	3	11	4	0	13	2	4	7	4

*Deafness excluded.

tuberculous meningitis at the beginning of therapy and had deafness and epilepsy as a residual. Three follow-up pneumoencephalograms showed no change.

Table III shows that most patients had normal ventricles, that is, fifteen out of twenty-seven.

Eight of the patients studied had ventricles which on measurement appeared to be within the upper limits of normal, and could not be classified as hydrocephalic (Fig. 9). Five of these cases were studied during therapy and three after completion of therapy.

Table IV shows the correlation between the findings on air studies and the mortality, duration of illness, stage at onset of therapy, presence of subarachnoid air, and age of patients. The highest mortality was observed in the patients with hydrocephalus. These patients also came to therapy in the more advanced forms of the disease, uniformly failed to show air in the subarachnoid space, and had more frequent neurological sequelae. No conclusion can be drawn from the age and

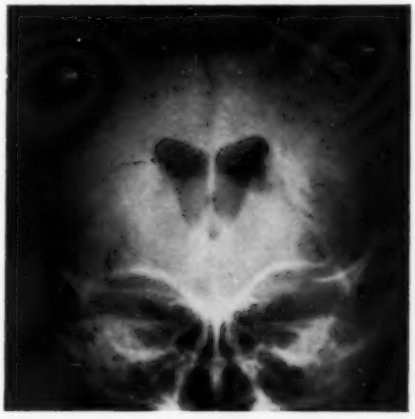

Fig. 9.—Pneumoencephalogram of a 3½-year-old male child on the fifth month of therapy for tuberculous meningitis. His physical and mental conditions are good except for deafness. The air study shows that the ventricles are of a size bordering between hydrocephalus and normal. There is a moderate amount of subarachnoid air.

TABLE V. CORRELATION OF DURATION OF THERAPY WITH RESULTS OF PNEUMOENCEPHALOGRAPHY

TIME INTERVAL BETWEEN ONSET OF THERAPY AND PNEUMOENCEPHALOGRAPHY	HYDROCEPHALUS		NO FILLING OF VENTRICLES		NORMAL	
	NO. TESTS	NO. PATIENTS	NO. TESTS	NO. PATIENTS	NO. TESTS	NO. PATIENTS
Less than 1 mo.	7	5			4	4
1 mo. to 5 mo.	7	3			8	6
6 mo. to 11 mo.	2	1	1	1	2	4
1 yr. to 23 mo.	0				1	1
2 yr. to 35 mo.	1	1				
3 yr. to 4 yr.			3	1	2	2
Total	17	10	4	2	17	17

duration of illness in the various groups.

Table V shows the time after the onset of the disease when the air studies were performed. Hydrocephalus as well as normal ventricles were encountered very early in the course of the disease, within the first month of therapy, and late after one year of observation.

Patients with active tuberculous meningitis tolerated pneumoencephalography well. The most common reaction observed was fever of three or four days' duration. The only fatality observed in this group of cases occurred in a 33-month-old boy (Patient 4, Table I) who was mentally retarded and had marked hydrocephalus. He died five days after a ventriculogram; at this time he was in the second year of observation after the onset of the meningitis.

DISCUSSION

During the early phase of tuberculous meningitis there occurs a hypersecretion of cerebrospinal fluid with distention of the cisterns and cerebral sulci. This facilitates the passage of air with unusually good filling on encephalography (Fig. 10). In a few patients the third ventricle may be distended sufficiently to cause a physiological block of the basilar cisterns. This can be determined by cisternography.[10] We did not demonstrate the condition, but feel sure that it occurred in some cases. Although the patient may appear critically ill, the patency of the basilar system favors a good prognosis. An exception is obstruction of the aqueduct where encephalography by the lumbar route would fail to fill the ventricles. Fortunately this is rare and occurred in only two of Lorber's cases. One of our patients, who showed no ventricular filling but adequate filling of the sulci, has done well. The other developed severe epilepsy.

In more advanced cases, exudate is formed predominantly in the basilar cisterns. Should the patient live long enough, secondary hydrocephalus occurs. The function of early therapy is to attempt to prevent this obstruction. The concept that some hydrocephalus invariably accompanies tuberculous meningitis already has been disproved.

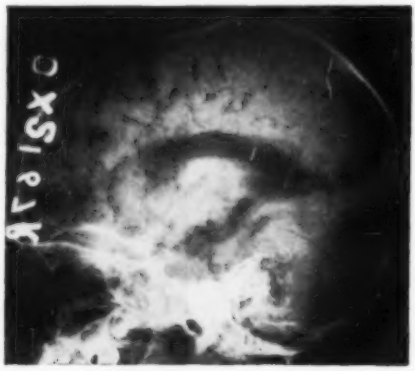

Fig. 10.—Pneumoencephalogram of a 2-year-old male infant on the ninth day of therapy for moderately advanced tuberculous meningitis. The ventricles are of normal size and there is an abundance of subarachnoid air.

In this series several patients were shown to have an entirely normal pattern after completion of therapy.

Whereas most of the patients with normal ventricular patterns will do well, only a few of the abnormals will survive and most of these will have neurological or mental defects.

It is apparent that although tuberculous meningitis involves the vascular system and is associated with encephalitis, the fatal outcome in many chronic cases is due to obstructive

hydrocephalus. It is hoped that with advancing studies and surgical treatment of hydrocephalus, many of these patients, at present lost, may be saved.

CONCLUSIONS

Pneumoencephalography should be performed in children with tuberculous meningitis when the progress, clinical or chemical, is unsatisfactory. The procedure is of great importance in evaluating the underlying pathological process and any modification in therapy.

The presence of obstruction in the basilar cisterns usually indicates a poor prognosis. In a few cases arrest of the hydrocephalus will occur spontaneously. Patients in whom the meningitis is arrested, but in whom the hydrocephalus is progressive, become problems of surgical management.

A normal pneumoencephalogram usually, but not always, indicates a good prognosis.

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Preventive Pediatrics

A few Weeks since the Operation for the Hare-Lip was performed to great Perfection on a young Man in Milton near Brush-Hill; and a Child in Boston has received as much Benefit from the Operation as the Case would admit of, by Mr. HALL, Surgeon to the 14th Regiment. The Impression these unhappy Sights are apt to make on married Women, should be an Inducement to have this Defect in Nature rectified early in Life, as there are numerous Instances of the Mother's affection having impressed her Offspring with the like Deformity.

NEW LONDON GAZETTE, September 14, 1770.

CONGENITAL AFIBRINOGENEMIA

Report on a Newborn Infant Without Fibrinogen

Burton J. Grossman, M.D., and Robert E. Carter, M.D.
Chicago, Ill.

THE congenital absence of fibrinogen is a rare occurrence; only thirty-one apparent cases have been reported to date.[1-27] This disease has been grouped by some authors under "inborn errors of metabolism."[29] Because of the rarity of the disease and the remarkable coagulation defects seen, this case is reported.

Since excellent recent reviews of the literature on congenital afibrinogenemia have appeared,[17, 18, 28] no attempt will be made in this paper to review the literature.

CASE REPORT

The infant, weighing 3,355 grams, was born to a 33-year-old gravida iv, para ii mother. The mother's Kahn test was negative and her blood type was A, Rh positive. The first stage of labor lasted 2 hours; the second stage lasted 1 hour 50 minutes. Delivery was accomplished under saddleblock anesthesia and was described by the attending physicians as being a "very difficult mid-forceps." The head was in the LOA position but had to be rotated to the LOT position in order to pass the outlet of the pelvis. The baby breathed and cried immediately.

Examination of the baby immediately after delivery revealed a mature, somewhat pale baby in acute distress. The child had tremors and rigidity of all the extremities and the cry was weak. There was considerable molding of the head, and the anterior and posterior fontanels were not palpable, due to overriding of the cranial bones. Forceps marks on the left and right cheeks and a laceration and cephalohematoma over the left parietal region were present. Both pupils were widely dilated and reacted only minimally to light.

Examinations over the subsequent four hours showed large retinal hemorrhages in the left eye and several smaller hemorrhages in the right. The abdomen was soft and the liver edge was felt 2 fingerbreadths below the right costal margin; the spleen was not palpated. The Moro response was symmetrical and considered normal. The chest was clear. At approximately 5 hours of age the baby appeared quite pale, and some bloody mucus was noted in the mouth. Respirations were irregular and were accompanied by grunting. The Moro reflex was hyperactive and there were marked tremors of the extremities.

A hemoglobin of 14 grams was obtained 2 hours 40 minutes after birth. The baby was given 5 mg. of vitamin K (Synkayvite) parenterally. Blood drawn for hematological study did not coagulate during the subsequent seventy-four-hour period, and was considered incoagulable. Prothrombin time was greater than 6 minutes, with a control of 20 seconds. When 80 INH units of thrombin were added to the whole blood, no clot formed, in contrast to immediate clotting by normal blood. When fibrinogen or normal whole blood was added to the infant's specimen, a clot formed. On smear the white blood count was considered

From the Department of Pediatrics and the Chicago Lying-In Hospital, University of Chicago.

to be within normal limits and numerous platelets were seen. There were 7 normoblasts per 100 white blood cells. No direct total white cell count or platelet count was performed. Both direct and indirect Coombs' tests were negative, and the infant's blood type was A, Rh positive.

A diagnosis of congenital afibrinogenemia was made. The umbilical vein was catheterized and 0.3 Gm. of purified human fibrinogen was given slowly. One-half hour afterward the clotting time on venous blood was 15 minutes.

Despite therapy the baby's condition continued to deterioriate and further neurological signs of increased intracranial bleeding developed. Large ecchymotic areas were noted on the skin. At approximately 12 hours after delivery the baby developed Cheyne-Stokes respiration, and despite whole blood transfusion, Adrenalin, and stimulants, the infant died at 13 hours of age.

Pathological Findings.—At autopsy there was no icterus and the skin appeared pale. There was a left parieto-occipital cephalohematoma, measuring approximately 7 by 5 by 2 cm. Within the deep layers of the scalp and within the fascial plane between the scalp and the calvarium there were multiple large (5 by 4 cm.) areas of hemorrhage. The fontanels, sutures, and calvarium were normal. Thirty-five milliliters of blood, half of which was clotted, was collected from the right subdural and subtentorial space. There was a large jagged tear in the right leaf of the tentorium cerebelli, but the falx cerebri was intact. A small laceration was noted in the left leaf of the tentorium and 15 ml. of mixed clotted and unclotted blood was removed. No subarachnoid or intracerebral hemorrhages were present. The brain appeared grossly normal and cut sections of the formalin-fixed brain revealed no focal lesions.

Small quantities of blood-tinged mucus were found in the mouth and pharynx. No free fluid was found in the chest, the ductus arteriosus was widely patent, the foramen ovale was open (1 to 2 mm.), and no anomalies of the heart or great vessels were noted. Both lungs floated in water and appeared grossly to be well aerated. There were multiple widespread ecchymotic hemorrhages involving the parenchyma of the lungs and the visceral pleura.

The peritoneal cavity was moist and appeared normal. The liver weighed 135 grams, was softer than usual, and was brownish tan. Over the mid-anterior portion of the left anterior lobe there was a soft depressed 2 by 1.5 cm. area of fine purple mottling beneath the capsule. The spleen weighed 9.5 grams, was firm, dark purple, with prominent lymphoid follicles and vascular markings. The gastrointestinal tract was in normal relation. The stomach was lined with red- and black-tinged, thick mucus. No hemorrhages were noted in the gastric mucosa. The remainder of the intestinal tract and its contents were normal. The urinary tract was grossly normal except for a small hemorrhage into the bladder mucosa. The adrenal glands were normal. The bone marrow of the sternum, ribs, and thoracic and lumbar vertebrae appeared abundant and normal in color.

Microscopic examination of the organs confirmed the grossly apparent hemorrhages.

Laboratory Studies.—The parents and two brothers of this baby were studied to determine if any other member of the family had a deficiency of fibrinogen. The methods employed in these studies included the Allen modification[30] of the Lee-White clotting time; antithrombin titer using the semiquantitative determination of Astrup and Darling[31]; sedimentation rate; electrophoretic determination of plasma fibrinogen; and a plasma-thrombin titration wherein 0.1 ml. of oxalated plasma (1.0 ml. of 0.11 M sodium oxalate to 9 ml. whole blood), and 1.0 ml. of various thrombin solutions (1 INH, 2 INH, 5 INH, and 10 INH units per milliliter) were added together and the clotting time measured.

The results of the whole blood clotting times, antithrombin titers, and sedimentation rates are shown in Table I. Of interest is the increase in whole blood clotting time in the father and the 4-year-old brother. The increase in clotting time in the 4-year-old brother is significant in itself, but more so when one considers the tissue trauma accompanying vena puncture in a child this age.

The normal values for the antithrombin titers measured by the Astrup and Darling[31] method vary a great deal from person to person. From experience in our laboratory all the values except for the one of 148 ATU per milliliter are within the normal range. The sedimentation rates of the father and 4-year-old brother of our patient are lower than are usually found in this laboratory.

TABLE I

	WBCT*	ANTITHROMBIN TITER	SEDIMENTATION RATE (WINTROBE -UNCORRECTED)
Patient	>3 days	86 ATU†/ml.	—
Mother	22 min.	110 ATU/ml.	33 mm./hr.
Father	40 min.	89 ATU/ml.	3 mm./hr.
4-year-old sibling	47 min.	128 ATU/ml.	1 mm./hr.
10-year-old sibling	—	148 ATU/ml.	—
Control	30 min.‡	94 and 115 ATU/ml.	Normal

*Whole blood clotting time.
†Antithrombin units.
‡Normal values for WBCT by method employed 25 to 35 min.

The results of the plasma thrombin titration are illustrated in Fig. 1. It is of interest that the father and the two brothers show clotting times of plasma thrombin mixtures which are greater than those seen for the mother and the control. The patient's plasma was incoagulable at all levels of thrombin.

All plasma protein electrophoretic separations were carried out using a filter paper strip technique in a Spinco* cell. A sodium barbital-barbituric acid buffer (pH 8.6) was used with a voltage of 130 volts and a current of 10 milliamperes. Samples were electrophorized for fourteen hours at this voltage. The paper strips were dyed after drying and were analyzed in a Spinco Analytrol.* Reproductions of the tracings are presented in Fig. 2. The curves represent the density of dye in the various portions of the paper strips.

Distinct fibrinogen peaks were identified in the samples from the mother, the 4-year-old sibling, the father, and in various control subjects. Only representative curves are reproduced. The fibrinogen peaks had a mobility between those of the gamma globulin and the beta globulin. A pure fibrinogen control sample had an identical mobility. No fibrinogen peak was seen in the electrophoretic pattern of the infant's blood. While under the experimental conditions employed, quantitation of the amount of fibrinogen present by measuring the areas under various peaks of the curve is subject to considerable uncertainty, such calculations were made. Total protein on the sample was determined by the biuret method. Values for fibrinogen calculated were: mother 0.89 gram, 4-year-old sibling 0.49 gram, father 0.77 gram, infant, no peak discernible. No sample for electrophoresis was obtained on the 10-year-old sibling.

In Fig. 2 the point of application of the plasma on the paper strip is indicated by an arrow. It is noted that a distinct accumulation of material staining as protein occurred at the point of application in each of the oxalated plasma samples studied. No such residual of material at the application point is found with serum samples, and it is assumed that the

*Registered trade name.

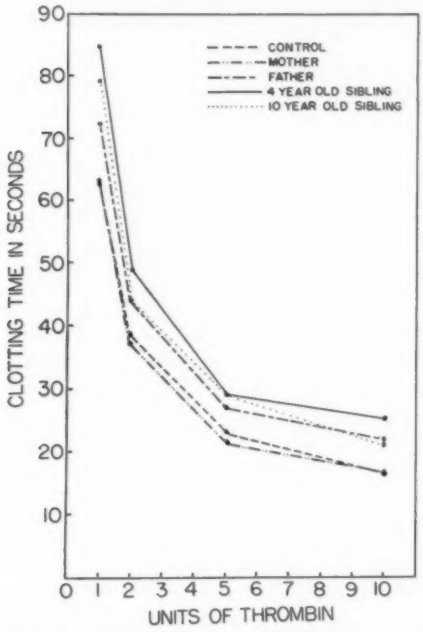

Fig. 1.—Results of clotting studies using graded amounts of thrombin.

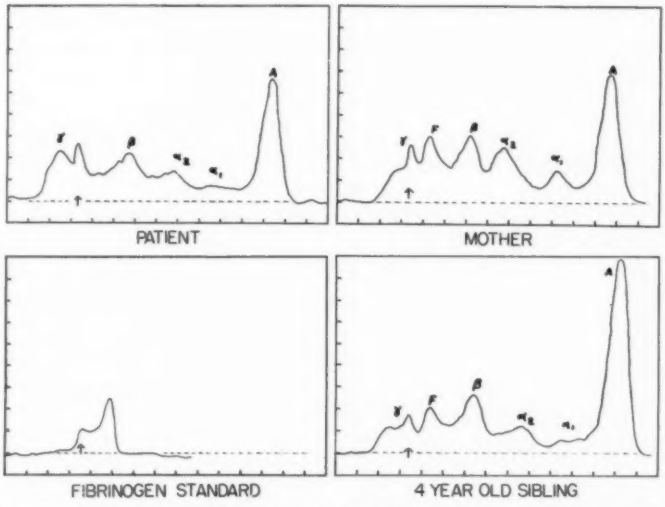

Fig. 2.—Results of paper-strip electrophoresis studies of plasma samples from patient and family.

oxalate treatment of the blood sample was responsible for this effect.

DISCUSSION

At the time of this writing thirty-one patients with apparent congenital afibrinogenemia have appeared. The most striking and characteristic finding in all patients is the incoagulability of the blood from birth. Despite this fact the hemorrhagic manifestations are frequently less severe than those seen in hemophilia.

The hereditary pattern of congenital afibrinogenemia has been given some attention.[17] Cousin marriages have appeared in the kinship of seven patients, occurring in parents or grandparents. Seven of the patients with congenital afibrinogenemia have had siblings with bleeding disorders. Only in the cases of Diamond and Barges[12] have the siblings been shown to have a proved afibrinogenemia. Four reports[13, 14, 16, 17] indicate hypofibrinogenemia in one or more relatives of the reported patients. In other families of patients with congenital afibrinogenemia the fibrinogen levels, when reported, have been normal.

In light of previous reports[13, 14, 16, 17] of hypofibrinogenemia in families of patients with congenital afibrinogenemia the family of our patient was studied. The data presented in Table I and Fig. 1 indicate a defect in the coagulation mechanism of the father and the two brothers of our patient. When thrombin is added to whole oxalated plasma the time required for a clot to form should depend principally on the amount of fibrinogen available for conversion to fibrin. The steps in the coagulation system leading to the formation of thrombin should not interfere with the final reaction. An increase in a circulating antithrombin could interfere with the amount of thrombin available for reaction with fibrinogen, thus increasing the time for formation of fibrin (which is the endpoint in the measurement of clotting time). The finding of normal levels of antithrombin in this family would argue against the assumption of an increased circulating antithrombin. Therefore, the increased clotting times of the father and two brothers indicate a reduction in fibrinogen. The reduction in the level of fibrinogen could not be clearly demonstrated by electrophoresis of the plasma.

The plasma-thrombin titration technique is simple and direct. At the levels of thrombin used the test seems to be sensitive to small differences in fibrinogen levels. Wagner[17] is quoted as stating that one-hundredth of the usual concentration of fibrinogen will eventually produce a clot. Brinkhouse and Wagner[32] considered the most sensitive technique for qualitative analysis of fibrinogen to be the use of a potent thrombin solution and direct observation of the plasma for a clot. It is probable that electrophoresis would not detect amounts smaller than 5 per cent of the normal, whereas a clot will form with approximately 1 per cent of the usual level.

The two brothers of our patient have been reported as having epistaxes but no other hemorrhagic manifestations. There is no history of bleeding in the father of our patient. With so few members of the total family studied for reduction in fibrinogen no hereditary pattern for this defect can be predicted in this case.

SUMMARY

1. A case of congenital afibrinogenemia in a newborn infant is presented.

2. The finding of a possible reduction in fibrinogen in the father and two brothers of the patient is reported.

3. The use of clotting techniques as a sensitive means of detecting fibrinogen deficits is discussed.

We are indebted to Dr. Edith Potter and to the members of the Pathology Department of the Chicago Lying-In Hospital for making the autopsy findings available for use in this report. We are also indebted to Dr. Albert Dorfman of the Pediatric Department of the University of Chicago for his assistance in interpretation of the data and suggestions on preparation of the manuscript.

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ENTEROBIASIS IN CHILDREN

The Use of Zinc Oxide Ointment Locally as a Therapeutic Agent*

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A NUMBER of oral treatment regimens[1-4] using varied drugs are available for the treatment of pinworm infestations. This study of Enterobiasis cases among American school children in Nagoya, Japan, was undertaken to observe the effect of zinc oxide ointment applied locally to the rectum. The use of an ointment was based on the assumption that breaking the cycle of self-reinfestation by preventing the adult females from laying their eggs on the perianal surface could effect a cure.

METHODS OF STUDY

Seventy-four children of both sexes, between the ages of 6 and 14 years, with positive pinworm slides were divided into three groups:

Group A: The first group of nineteen children, together with all children and adults of their respective households, were treated with syrup of Antepar,† one teaspoonful twice daily for eight days. After an interruption of therapy for one week, Antepar was again given for eight days in the same dosage.

Group B: Twenty-five children and all members of their immediate families received liberal applications of zinc oxide ointment‡ to their rectums three times daily and at bedtime for twenty-one days.

Group C: Thirty children received no treatment.

Twenty-five days after the institution of treatment, three consecutive morning pinworm slides, taken before the bath, were examined. In the case of the children who were not treated, slides were examined approximately twenty-five days after the pinworm infestation was discovered.

Three consecutive negative slides were considered evidence of cure.

RESULTS

Results of treatment are shown in Table I and Fig. 1. Seven of the thirty children who received no treatment had spontaneous cures. Of the nineteen who received syrup of Antepar, 89.5 per cent responded successfully to treatment. Twenty of twenty-five children treated with local zinc oxide ointment as outlined under methods were cured.

Table I. Results of Treatment

TYPE OF TREATMENT	NUMBER TREATED	NUMBER CURED	PERCENTAGE CURED
A. Syrup of Antepar	19	17	89.5
B. Zinc oxide ointment	25	20	80.0
C. None	30	7	23.3

DISCUSSION

The prevention of reinfestation or retrofection[5] in individuals harboring

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*Opinions expressed herein are those of the author only and do not necessarily reflect the opinions of the United States Air Force.

†Piperazine citrate.

‡Zinc oxide ointment was applied in approximately a one-eighth inch thickness over the rectal orifice and perianal folds. The ointment was not instilled into the rectum itself.

pinworms is an important consideration in treatment. Since the life cycle of *Enterobius vermicularis* is quite short (around fifteen days), no treatment would be necessary if ova or larvae did not repeatedly gain entrance into the body. Actually the parasites would die of old age in short order.

In view of the fact that reinfestation or retrofection is necessary for the perpetuation of pinworm infections, and that the female of the species ovulates outside the body on the perianal surface, it seems reasonable to assume that the 80 per cent cure rate of the zinc oxide method of treatment herein reported is due to an obstruction to self-reinfestation. Since zinc oxide has no known toxic effect against the pinworm, it is suggested that zinc oxide ointment, as well as any other nonirritating ointment, may be used locally as an adjunct to established treatment of pinworm infestations.

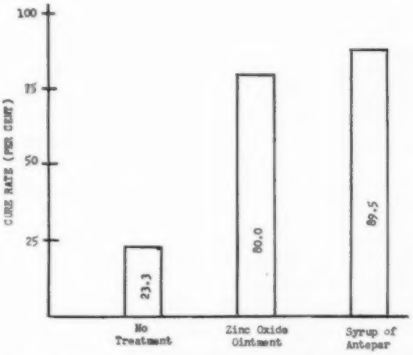

Fig. 1.—Percentage cures after one course of treatment.

SUMMARY

The use of zinc oxide ointment applied locally to the rectum three times daily and at bedtime in the treatment of pinworms has been described. Eighty per cent of twenty-five children so treated were cured compared to an 89.5 per cent cure rate in nineteen children treated with syrup of piperazine.

I wish to thank T/Sgt. Alva T. Kershaw who kept all the records for this study, 1st Lt. Frank H. Dowell for his helpful suggestions, and M/Sgt. William W. Wright, S/Sgt. Joseph B. Zeoli, and A/2C Lloyd D. Tripp who examined all the slides before and after treatment.

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PRETIBIAL FEVER DUE TO LEPTOSPIRA POMONA

Report of Two Cases in Siblings

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In 1952 evidence was presented that the clinical syndrome "pretibial fever" or "Fort Bragg fever" was due to infection with *Leptospira autumnalis*.[1] Recently we have had the opportunity to study two brothers with the clinical picture of pretibial fever and in whom there was evidence of infection with *Leptospira pomona*. These are apparently the first reported cases of pretibial fever in which *L. pomona* has been indicted as the causative agent.

CASE REPORTS

Willie B., aged 8 years, and Kenneth B., aged 6 years, brothers, were admitted to the pediatric service of the Vanderbilt University Hospital with the referring diagnosis of acute poliomyelitis. Because their hospital courses were virtually identical, they will be described together.

Both children were well until forty-eight hours prior to admission, when Kenneth developed anorexia, malaise, and fever. Within a few hours Willie developed similar symptoms and for twenty-four hours prior to admission both exhibited lethargy, increasing fever, myalgia, headache, and vomiting. Because of the development of nuchal rigidity and generalized weakness, the family physician was consulted, who referred the patients to this hospital.

The family lived on a farm and the patients frequently swam in a stagnant pond where hogs watered. They had last been swimming eight days prior to admission. Past and family histories were otherwise not pertinent.

Physical examination of both children on admission was identical. Both were acutely ill, febrile, and lethargic but were well oriented. The skin was flushed and dry but free of rash. Both exhibited nuchal rigidity and other signs of meningeal irritation. There was no splenomegaly. Mild muscle tenderness was present. All reflexes were intact and there was no demonstrable cranial nerve palsies or muscle weakness. Blood pressures were within normal limits. Their clinical courses are depicted in Fig. 1 and pertinent laboratory data are recorded in Table I.

Because of signs of meningeal irritation and the referring diagnosis of poliomyelitis, lumbar punctures were immediately performed, but the spinal fluid was found to be entirely normal. The urine was then examined and the diagnosis of leptospiral disease was first entertained following the demonstration of proteinuria and microscopic hematuria.

On the third hospital day both children developed a marked conjunctivitis and a skin rash over the pretibial areas bilaterally. This eruption consisted of numerous erythematous, maculopapular areas which resembled erythema nodosum. These lesions faded rapidly and completely disappeared within forty-eight hours.

Both boys became afebrile within forty-eight hours after admission; however, on the fifth hospital day both developed fever up to 101° F. and 102° F. At that time a repeat

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lumbar puncture on Kenneth revealed 29 mononuclear cells, normal spinal fluid sugar and protein, and sterile cultures. Spinal fluid from Willie at this time was entirely normal.

A gastrocnemius muscle biopsy from Willie on the ninth day of illness revealed no significant abnormalities. Dark-field microscopy of the blood of both children on the fourth hospital day and several blood cultures failed to reveal any leptospira. Both patients became afebrile by the seventh hospital day and were discharged three days later in good condition.

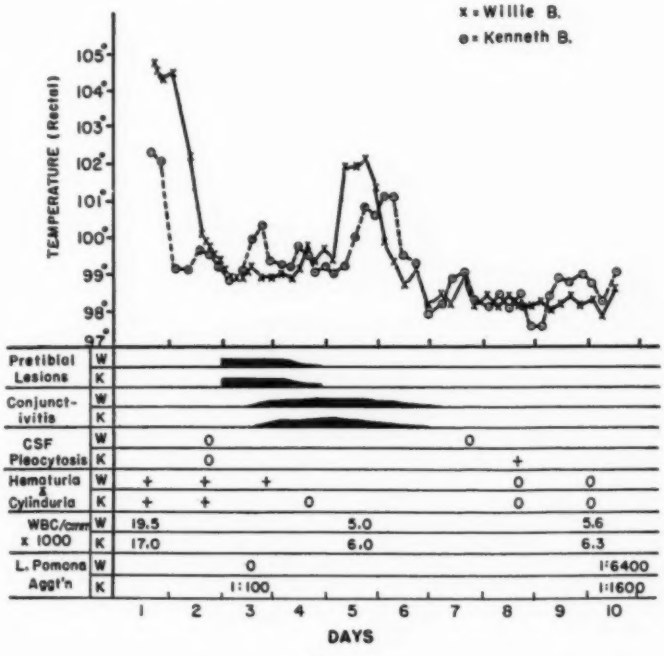

Fig. 1.

The agglutination-lysis titers against *L. pomona* are presented in Fig. 1 and Table I. The family moved from this area shortly after discharge, preventing further serological studies.

DISCUSSION

Pretibial fever was originally observed during the summer of 1942 in troops stationed at Fort Bragg, N. C. Forty cases occurred during the summer months of that year and approximately the same number were diagnosed during each of the following two summers. The disease as described by Daniels and Grennan[2] was a nonfatal febrile illness of approximately five days' duration, characterized by relatively sudden onset of fever, malaise, generalized aching, headache, and splenomegaly. The most distinctive feature of the illness was the appearance of an erythematous, maculopapular rash appearing usually on the fourth day of illness and peculiarly localized to the anterior aspects of the legs, which suggested the name "pretibial fever." The lesions were raised, warm,

slightly tender and in many cases resembled erythema nodosum. There were no complications and at the conclusion of the fever all patients recovered and were able to return to their duties.

viral and rickettsial agents. The possibility that this agent might be a leptospira was considered several times but results obtained by methods then employed failed to support this hypothesis.

TABLE I. LABORATORY DATA*

	WILLIE B.	KENNETH B.
Urine:		
Albumin	Trace	Trace
RBC/h.p.f.	1-4	4-8
WBC/h.p.f.	6-12	20-25
Casts/h.p.f.	1-2	1-4
Blood:		
Hemoglobin (Gm./100 ml.)	12.5	12.5
Leukocytes per c.mm.	13,650	17,000
Neutrophils (per cent)	78	86
Sedimentation rate (Wintrobe)	39/28	51/30
Bilirubin (direct/total) (mg./100 ml.)	0.1/0.2	0.0/0.2
Cephalin flocculation 24 hr.	Neg.	Neg.
48 hr.	1+	1+
Cholesterol (mg./100 ml.)	175	210
Spinal fluid:		
	(5)†	(6)†
Leukocytes per c.mm.	0 ⟶ 0	0 ⟶ 29
Protein (mg./100 ml.)	15 ⟶ 17	15 ⟶ 17
Sugar (mg./100 ml.)	73 ⟶ 51	53 ⟶ 77
Agglutinations:		
Typhoid	Neg.	Neg.
Paratyphoid	Neg.	Neg.
Brucella	Neg.	Neg.
Tularemia	Neg.	Neg.
Heterophil	Neg.	Neg.
Cultures:		
Throat	Neg.	Neg.
Blood	Neg.	Neg.
Urine	Neg.	Neg.
Stool	Neg.	Neg.
Leptospira agglutination:		
	(7)†	(7)†
L. pomona	0 ⟶ 1:6,400	0 ⟶ 1:1,600
L. autumnalis	1:100 ⟶ 1:6,400	1:100 ⟶ 1:400
L. icterohaemorrhagicae	0 ⟶ 1:100	0 ⟶ 1:400

*Admission findings unless otherwise stated.
†Interval in days between determinations.

From the blood of one of the acutely ill patients in 1944, an infectious agent was recovered which produced a fatal illness in hamsters, a mild febrile illness in guinea pigs and rabbits, and grew well in embryonated eggs.[3] However, various types of studies failed to reveal any relationship to a number of the more common

It was not until 1951 that Gouchenour and co-workers[1] at the Army Medical Service Graduate School reexamined acute and convalescent sera from soldiers who had recovered from Fort Bragg fever nine years previously and demonstrated high levels of agglutinating antibodies against *L. autumnalis*. Stored, frozen, paired

sera from five of the original soldiers ill with pretibial fever showed agglutination titers against *L. autumnalis* ranging from 1:1,600 to 1:25,600. Subsequently, the leptospiral organism was recovered from the two-hundred fifty-ninth hamster passage of the Fort Bragg agent. Extensive cross-agglutination tests then indicated that Fort Bragg fever was essentially the same disease as autumnal fever which was prevalent in Japan and the Far East. Members of this group of leptospira were not previously known to exist in the United States; however, since that time evidence of infection with *L. autumnalis* has been demonstrated in other patients with the clinical picture of pretibial fever.[4] No cultural or serological evidence of infection with any of the other strains of leptospirae has been reported in patients with this clinical syndrome.[4]

A thorough search of the literature failed to reveal any previously reported cases of Fort Bragg or pretibial fever occurring in childhood.

In the present report, both patients gave a history of swimming in a stagnant pond where hogs watered and both exhibited the typical pretibial lesions beginning on the fourth or fifth day of the illness. In addition, both exhibited proteinuria, hematuria, conjunctivitis, and one (K. B.) developed aseptic meningitis. Neither patient exhibited jaundice or abnormal liver function. No leptospirae could be found on direct microscopic examination of the blood; however, Beeson and Hankey[12] have never been able to demonstrate the organisms by this method in well-documented cases of leptospirosis. Both children exhibited a marked rise in agglutination-lysis titer against *L. pomona* in paired serum specimens obtained on the third and tenth hospital days. The elevations in titer against *L. autumnalis* and *L. icterohaemorrhagicae* were felt by Gochenour[5] to represent nonspecific cross immunological reactions.

Serum from a 12-year-old sibling, James B., revealed an agglutination-lysis titer of 1:100 against *L. pomona, L. icterohaemorrhagicae,* and *L. sentot.* He had also been swimming in the same pond and experienced a mild febrile illness without pretibial lesions. Sera from another sibling and both parents, none of whom had been swimming in the pond, were negative against seventeen leptospira screening antigens.

For many years it has been recognized that numerous pathogenic strains of leptospirae exist. At least thirty serologically different leptospiral strains have been isolated.[6a, b] However, only in recent years has it been recognized that several less well-known leptospiral strains are widespread in domestic animals in the United States and that these are not uncommonly transmitted to man. At present, six different strains of leptospira productive of specific clinical syndromes in human beings have been isolated in North America: *L. icterohaemorrhagicae,* Weil's disease; *L. canicola,* canicola fever; *L. autumnalis,* pretibial or Fort Bragg fever; *L. pomona,* swineherd's disease; *L. bativiae,* Indonesian fever; and *L. grippotyphosa,* swamp fever.[7]

L. pomona was first isolated and identified from the blood of a dairy farmer in Pomona, Australia, in 1936.[8] Since that time, this agent has been reported throughout Australia, in Europe, and for the past six years in the United States as being the cause of a nonfatal influenza-

like illness with fever, headache, myalgia, conjunctivitis, and, not uncommonly, aseptic meningitis. A biphasic fever curve, such as occurred in the presently reported cases, is more commonly noted in reports from Europe than from this country.[8, 9] Jaundice is characteristically absent and the urine usually exhibits protein and red blood cells. As in other types of leptospirosis, iridocyclitis is an occasional sequela.[10] For many years the disease was found to be associated especially with pig tenders—thus the name swineherd's disease.[11] In the United States cows and hogs are the animal vectors, the organisms being contained in the renal tubules of animals and excreted in the urine. To infect a human being, it is necessary for the spirochete to enter the body through the mucous membranes or a skin abrasion.[4] Either portal of entry is conceivable in our patients as both had numerous cutaneous abrasions and swam in a stagnant pond frequented by hogs.

Meningeal involvement is unusual in infections due to *L. autumnalis*, whereas splenomegaly and a striking leukopenia are the rule.[13] Meningeal irritation may be present in many of the different types of leptospirosis, including that due to *L. icterohaemorrhagicae* but is most commonly seen in infections due to *L. pomona*.[13, 14]

SUMMARY

Two siblings with the clinical picture of pretibial or Fort Bragg fever and serological evidence of infection with *L. pomona* are presented. These patients represent the first cases known to us in which this clinical picture, previously reported only with infection with *L. autumnalis*, has been associated with evidence of infection by *L. pomona*. These patients also apparently represent the first reported cases of pretibial fever occurring in childhood.

Acknowledgment is due to Lt. Col. William S. Gochenour, Jr., and his staff at the Army Medical Service Graduate School, Washington, D. C., for performing the leptospira agglutinations, and to Miss Ann Hudgens and Miss Mally Eastham for the preparation of the manuscript.

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CUTANEOUS MONILIASIS IN INFANTS

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THE increasing incidence of cutaneous moniliasis in adults has been associated with the widespread use of the broad-spectrum antibiotics and their effect on the normal intestinal flora[1] and possibly the normal flora of the skin. This theory may not be logically applied to *Candida albicans* infections of the skin in infants who have never received antibiotic therapy or whose mothers did not receive antibiotic therapy during pregnancy.

Although the pathogenesis of infantile cutaneous moniliasis is unexplained, the importance of recognizing the clinical symptoms is emphasized by Dobias,[2] who feels that the condition "is probably not as rare or always as benign as most commonly considered." The present communication deals with the prevalence of *C. albicans* infections, descriptions of the types which I have seen, and the treatment.

During the past three years I have observed 130 infants with eruptions of the genitocrural area (diaper area). From forty-six of these, *C. albicans* was cultured and considered to play some role in the course of the condition. These data should not be interpreted as being indicative of the general incidence of disease, but as representative only of the type of patient seen in one dermatologist's experience in a given period of time.

All of the children with *C. albicans* infections who had been seen previously by general physicians or pediatricians had been diagnosed as having "diaper rash" or "infantile eczema." This failure to recognize and differentiate specific objective symptoms prompted the discussion in the following paragraphs.

Of the several types of eruptions which affect the lower abdomen and genitocrural areas, those which offer the greatest difficulty in differential diagnosis are uncomplicated infantile eczema (atopic), infantile eczema complicated by superimposed infection with *C. albicans,* and primary cutaneous moniliasis.

Table I outlines the major differential points which facilitate diagnosis and aid in directing therapy.

These differential diagnostic criteria are illustrated in Fig. 1 which shows all three conditions.

Infantile eczema usually appears shortly after birth and follows a course of remissions and exacerbations. There is frequently a familial history of allergic conditions, and also frequently a history of onset when citrus juices, eggs, or other allergens are included in the infant's diet. When a *C. albicans* infection is superimposed on this eczema, there is usually a sudden exacerbation which the parents

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may describe as "different from the usual flares" which they have seen. Primary *C. albicans* infection, or cutaneous moniliasis, is sudden in onset and may run a fulminating course.

There is generally a widespread distribution of lesions in infantile eczema, with the flexures heavily involved. Scaling in the scalp may be pronounced. The genitocrural region is frequently severely involved, because of the warmth and moisture in the

C. albicans infections included in this study, only three had any evidence of oral involvement, six had lesions in the axillae, and one had a generalized eruption which resembled ichthyosis, except for several clear areas.

One of the most important steps in the diagnosis of any dermatologic condition is the finding of the primary lesion. Usually a careful search in the periphery of the lesions of infantile eczema will reveal the characteristic

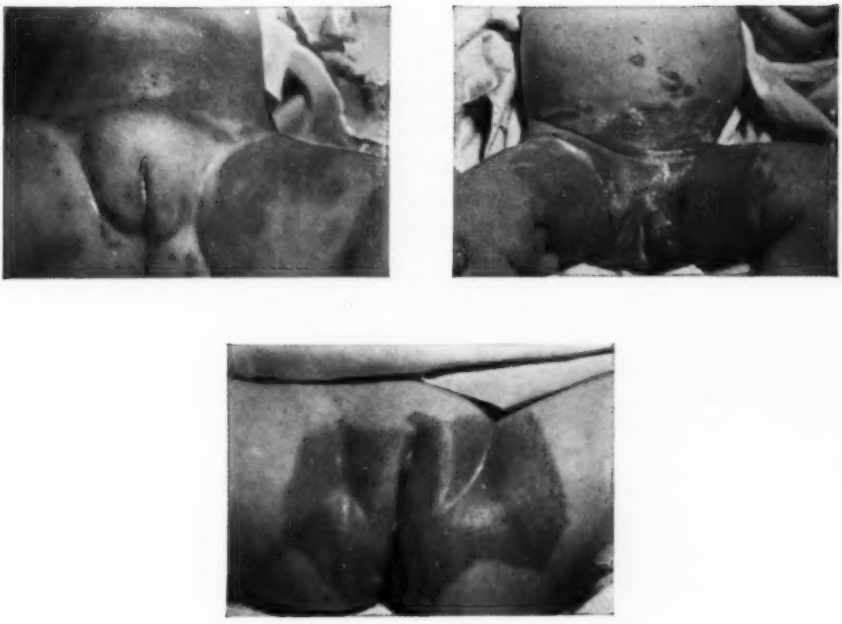
TABLE I. DIFFERENTIAL DIAGNOSIS OF INFANTILE ECZEMA, INFANTILE ECZEMA SECONDARILY INFECTED WITH CANDIDA ALBICANS, AND PRIMARY CUTANEOUS MONILIASIS OF THE GENITOCRURAL REGION OF INFANTS

	INFANTILE ECZEMA	INFANTILE ECZEMA PLUS INFECTION WITH C. ALBICANS	PRIMARY CUTANEOUS MONILIASIS
Duration	Chronic	Chronic with sudden flare	Acute onset
Distribution (usual)	Generalized	Generalized	Limited
Primary lesion	Follicular papule	Follicular papule	Scaly macule or vesicle
Definition of lesions	Ill-defined	Mixture of ill-defined and well-defined lesions	Well-defined
Color	Pink to dull red	Ill-defined lesions pink or dull red; well-defined lesions bright red	Bright red or yellowish red
Scaling	Diffuse	Diffuse	Most pronounced in periphery of lesions
Treatment	Elimination diets, local application of coal-tar preparations, sedatives, steroids	Candida infection first cleared, then treat eczema	Nystatin or gentian violet

area and irritation from urine and feces and occasionally the detergent used in washing the diapers, sometimes making it difficult to distinguish from contact dermatitis or "diaper rash." These irritating factors are probably conducive to superimposed secondary infections with bacteria or *C. albicans*. Bacterial infections (superficial pyodermas) are easily diagnosed by the presence of pustules or shallow ulcerations. Primary cutaneous moniliasis is usually limited to the genitocrural area. Of the forty-six infants with

follicular papule. These may be seen in child A of Fig. 1. In spite of the bright red color of most of the lesions in child B, there will be seen the small red papules, which are absent in child C. The presence of these follicular papules implies the atopic origin of the eczematous lesions.

Lesions of infectious origin are, in general, well defined, while eczematous lesions are almost invariably ill-defined. Superimposed infectious processes on eczematous conditions alter the appearance so that the lesions may



A. *B.* *C.*

Fig. 1.—*A*, Infantile eczema. *B*, Infantile eczema with superimposed *Candida albicans* infection. *C*, Primary *C. albicans* infection (cutaneous moniliasis).

appear to be partially to well defined, or there will be a mixture of well-defined and ill-defined lesions as seen in Fig. 1.

To many observers, slight differences in color are difficult to detect. To the trained dermatologist, the color of a lesion may represent an important clue to diagnosis. The lesions of infantile eczema are pink to dull red according to the age of the lesions, while cutaneous moniliasis lesions assume a bright red color, with sometimes a yellowish tinge such as is apparent in child C.

Scaling is profuse in the usual eczematous lesion, while it is more pronounced in the periphery of the infectious lesions of moniliasis. Eczematous scales are small and may be piled up to form crusts, while the moniliasis scales frequently are larger and tend to peel as seen in child C.

The purpose of any differential diagnostic study is to enable the clinician to arrive at a definitive diagnosis so that he may direct therapy to the best advantage of the patient. It is not within the scope of this communication to discuss the treatment of infantile eczema, but a far less controversial subject is the treatment of cutaneous moniliasis, which has seen several major advances during the past few years.

The old and still useful, but messy gentian violet has been complemented and almost superseded by more recent modalities, including the fatty acid derivatives such as undecylenic acid and antibiotics such as nystatin.

Nystatin is an antifungal antibiotic derived from *Streptomyces noursei* and is available in an ointment containing 100,000 units per gram, and a suspension for oral administration containing 100,000 units per cubic centimeter. Other preparations of the compound are useful in adult moniliasis but were not used in this study.

The same treatment regime was used for primary cutaneous moniliasis and infantile eczema with superimposed *Candida albicans* infection. The ointment was applied three times daily to all involved areas and 1 c.c. of suspension was administered by dropper four times daily. Improvement began almost invariably within the first week of treatment, and forty of the forty-six infants were clinically well within two to six weeks after treatment was instituted. Combined systemic administration of the suspension and local application of the ointment was superior to treatment with ointment alone.

SUMMARY AND CONCLUSIONS

Criteria are presented for the differential diagnosis of infantile eczema, infantile eczema and superimposed *Candida albicans* infections, and primary infections with *C. albicans* (cutaneous moniliasis).

Treatment of secondarily infected eczema consists of control of the infection before treating the eczema.

A brief discussion of the treatment of cutaneous moniliasis is presented.

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DYSPLASIA EPIPHYSIALIS MULTIPLEX

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A DISEASE entity seen in children and young adults and characterized by dwarfism, stubby digits, and roentgenologic evidence of mottling and irregularity in density and outline of multiple growing epiphyses has been described by several authors under different and, we feel, confusing terms since 1912. The varying array of nomenclature includes chondrodystrophia or achondroplasia,[23] atypical achondroplasia or osteochondropathia multiplex,[11] dwarfism with stippled epiphyses,[3] epiphysial dysostosis,[14] epiphysial dysplasia,[7] hereditary deforming dyschondroplasia,[10] and epiphysial dysplasia punctata.[18] Sir Thomas Fairbank[8] in 1947 gave the disease the name dysplasia epiphysialis multiplex which is now the generally accepted term. The syndrome, though seen in children, has never been described in American pediatric literature. However, European pediatric publications, as well as roentgenologic and orthopedic journals here and abroad, contain several reports.

CASE REPORT

T. M. (No. 8412-56), a 6-year-old Puerto Rican male, was admitted to the pediatric service on April 30, 1956. He had been complaining of periodic pains in both knees for two years. These episodes lasted a few days and were not severe enough to prevent him from playing and walking. However, during the two years prior to admission, he had a constant limp. No symptoms referable to the hips had been noted. Infancy and early childhood were not remarkable. His mental, emotional, and physical development was not considered to deviate from the normal. The child was one of binovular twins born by a spontaneous delivery. There are five children in the family; one has pulmonary tuberculosis. Three, including the other twin, are normal. The parents are living and healthy. No history of consanguinity was elicited. Physical examination on admission showed a 6-year-old boy who appeared to be somewhat stunted in growth and the measurements were as follows: height, 37 inches (average 46.3 inches); sitting height, 19½ inches; crown to umbilicus, 17¼ inches; umbilicus to heel, 19¾ inches; arm span, 39½ inches; and weight, 33 pounds (average 48.3 pounds). Examination of the hips, knees, and ankles did not disclose any swelling, irregularity, restriction of movements, or pain on manipulations. The examination of other systems failed to reveal any pathologic findings. The laboratory data were as follows: hemoglobin, 12.5 grams per 100 ml.; erythrocytes, 4,500,000 per cubic millimeter; hematocrit, 44 per cent; leukocytes, 14,000 per cubic millimeter; polymorphonuclears, 55 per cent; lymphocytes, 47 per cent; erythrocytic sedimentation rate (Wintrobe), 17 mm. in 1 hour

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Fig. 1. Fig. 2.

Figs. 1 and 2.—Roentgenograms showing irregularity in contour and calcification of both humeral hands. The right glenoid shows cystic changes. Note the irregularity of carpal bones and the heads of metacarpals.

Fig. 3. Fig. 4.

Figs. 3 and 4.—Roentgenograms of lower extremities showing deformed femoral heads and irregular contour of acetabulae and the condyles of the femora and tibiae.

(normal 0 to 10 mm.); blood Wassermann, negative; serum calcium, 10.5 mg. per 100 ml. (normal 8.5 to 11.5 mg.); serum phosphorus, 5.5 mg. per 100 ml. (normal 5 to 6.5 mg.); serum acid phosphatase, 2 Gutman units (normal 0.5 to 3 units); serum alkaline phosphatase, 16.1 units (normal 3.5 to 13 units); blood uric acid, 3.1 mg. per 100 ml. (normal 2 to 5 mg.); serum cholesterol, 127 mg. per 100 ml. (normal 140 to 250 mg.); cholesterol esters, 100 mg. per 100 ml. (normal 70 to 125 mg.). Urinalysis was normal. An iodine uptake of I^{131} by the thyroid gland in twenty-four hours was 75 per cent, which, according to our standards, is within the hyperthyroid range and for which there is no explanation. The patient has been under observation for six months after discharge from the hospital. The clinical and radiological findings are the same as noted previously.

Radiologic Findings.—Both humeral heads appear irregular in contour and calcification. Cystic changes are noted in the right glenoid. The carpal and tarsal bones are irregular both in contour and calcification. There is an epiphysis for both femoral heads as well as condyles. The epiphyses of the heads of femora are irregular in appearance. The femoral heads are deformed and the epiphyses united. The acetabula show irregular contour. The epiphyses of the heads of the metacarpals and metatarsals are also irregular. Cervical, thoracic, and lumbosacral spines reveal no evidence of osseous or articular pathology. The vertebrae and pelvis are normal. The skull shows no abnormality. Radiographic examination of

Fig. 5.—Roentgenogram of feet showing the irregular contour and calcification of the tarsal bones and heads of metatarsals.

the chest reveals normal cardiac and pulmonary findings. A complete radiologic survey of the skeletons of the parents and siblings reveals no abnormalities. The roentgenograms were reviewed by Dr. John Caffey who made a diagnosis of dysplasia epiphysialis multiplex (personal communication).

COMMENT

The etiology of dysplasia epiphysialis multiplex is unknown. It is presumed that there is some interference in the normal development of epiphysial cartilage which is a result of a disturbance of the enzyme phosphatase. The latter is involved in the normal deposition of minerals in bones. Calcium, phosphorus, and vitamin D must be available in adequate supply if normal bone growth is to be achieved. Additional factors in this growth mechanism are endocrines, osteoclasts, and the periosteum.[7] The role of genetics in this condition should be considered since there are many reports of familial occurrence. However, most of the reports do not record more than one member of the family. Consanguinity is not a factor. Pathologic examination of the bones has only been described in a few instances. Jansen[14] found mucoid degeneration in a section of the lower end of the femur. It is unfortunate that the epiphyses in this and other cases have not been examined.

A great majority of cases are seen in children and young adults. Nevertheless, Shephard[22b] describes cases in two adults 71 and 80 years of age and Gardiner-Hill[10] in an infant of 19 months. Both sexes are about equally affected. There are several instances of hereditary and familial occurrences.[22] Difficulty in walking or pain in and limitation of movements of the hips and knees is the usual initial complaint. Adults have arthritic symptoms. The intelligence is normal in most of the cases. Fairbank[9] cites two children with subnormal intelligence. Dwarfism of the short-limb type, repeatedly stressed as a distinguishing feature, is not an invariable manifestation. Epiphysial enlargement, short stubby fingers, and thumbs with blunt ends are not constant findings although believed to be so by many authors. Various skeletal deformities are found associated with the syndrome. Thus subluxation and limitation of joint movements with extension and flexion deformities, genu valgum, genu varum, dislocations, and spinal abnormalities have been observed.[8]

The characteristic roentgenologic abnormality observed in this syndrome is the irregularity in ossification of the epiphyses. Ossification centers may be underdeveloped and late in appearance with delayed union of the shafts. The density and shape of the epiphyses are irregular and appear mottled—mulberry-like outline.[9] There are areas of peripheral and central stippling of the epiphyses. However, the stippling is not as pronounced as is observed in cases of dysplasia epiphysialis punctata. The latter condition has stippling of the epiphyses but their outlines are regular. If serial x-ray examinations are done, improvement in radiologic appearance of the epiphyses is normally seen after several years, although the periphery of the epiphyses usually does not return to normal and may be irregular permanently. These roentgenologic findings are widespread, involving most frequently the hips, shoulders, ankles, and knees.

Changes in the heads of the femora and humeri are often observed. Less commonly, changes are noticed in the acetabulae, patellae, fibulae, greater trochanters, and femoral condyles. The ankles reveal marked obliquity due to the diminution in depth of the lower tibial epiphyses. The metaphyses are ordinarily not involved. The shafts of the long bones are often short but not usually thickened. The carpal and tarsal bones ossify late and may be irregular in outline. The metacarpals, metatarsals, and phalanges are stunted. Their epiphyses may reveal the characteristic irregular outline and stippling. Vertebrae, skull, and teeth are usually normal. The syndrome must be differentiated from achondroplasia, hypothyroidism, chondrodystrophies, endocrine conditions, congenital dwarfism, osteochondrosis juvenilis, cretinoid epiphysial dysgenesis, and hypopituitary dwarfism.[8]. The characteristic roentgenologic findings in the epiphyses distinguish dysplasia epiphysialis multiplex from other conditions. There is no treatment available which will influence the course of this disease.

SUMMARY

A case of dysplasia epiphysialis multiplex in a 6-year-old male child is recorded. There is no specific etiologic factor responsible for this syndrome. The irregularity of the epiphysial outline combined with stippling is a distinguishing diagnostic feature which is observed in multiple bones. The ultimate prognosis is for a spontaneous recovery from the symptoms and for a restoration of normal function. Some roentgenologic findings may persist after many years. Treatment does not influence the course or ultimate outcome of this condition.

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The Falling Evyll Called in the Greke Tonge Epilepsia

Not only other ages but also lytle chyldren, are oftentimes afflicted, with this grevous syckenes, sometyme by nature receyved of the parentes, and than it is impossible, or difficile to cure, sometyme by evyll and unholsome diet, wherby there is engendred many colde and moyst humours in the brayne, whereupon this infirmity procedeth, whiche if it be in one that is young and tender, it is very hard to be removed, but in them that are somwhat strong, as of seven yeares and upwarde, it is more easy.

I fynde that many thynges have a natural vertue against the falling evil, not of any qualitie elementall, but by a singular propertie, or rather an influence of heaven, whiche almyghtye God hath geven unto thinges here in earth, as by these and other.

Saphires, smaragdes, red coral, piony, mystletow of the oke, taken in the moneth of Marche, and the moone decreasying, tyme, savein, dylle, and the stone that is founde in the bellye of a yong swallow, being the first brode of the dame.

These or one of them, hanged about the necke of the chyld, saveth and preserveth it from the sayd sickenes. Now wil I describe some good & holsome medicines to be taken inward for the same disease.

If the childe be not very young, the mawe of a leveret, dronken with water and hony cureth the same. . . .

THOMAS PHAIRE. THE BOKE OF CHYLDREN, 1544.

CONGENITAL UNILATERAL MULTICYSTIC KIDNEY ASSOCIATED WITH MATERNAL RUBELLA

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THE removal of a unilateral cystic renal mass in the neonatal period has in the past led to a diagnostic and prognostic dilemma. The problem has been largely resolved by the recent reports of cases of congenital unilateral multicystic kidney in the medical literature.

Of greatest importance is the increasing recognition that this entity is etiologically, therapeutically, and prognostically unrelated to congenital polycystic kidney disease. In the presence of a normally functioning contralateral kidney, the mass may be extirpated with reasonable assurance of a normal life span. The following case is illustrative of this condition. Unique is the association here of maternal rubella in the first trimester of pregnancy.

CASE REPORT

A male infant weighing 3,180 grams was delivered with the aid of low forceps on Nov. 30, 1955, at the United States Naval Hospital, Newport, R. I. The mother, a 22-year-old primigravida, was diagnosed by her family physician as having rubella at about 2 months' gestation. The family history was noncontributory.

During the first examination on the day of birth a mass was discovered in the left upper abdomen. It was considered to be multicystic and of renal or possibly mesenteric origin. Transillumination was only suggestive of a fluid-filled mass.

Laboratory Studies.—Preliminary roentgenograms demonstrated a density which displaced the bowel forward and medially. An intravenous pyelogram, utilizing 6 c.c. of Neo-Iopax, visualized a normal calyceal grouping on the right. There was a vague suggestion of distorted calyces on the left but these were interpreted to be only bowel markings. The bladder was increasingly opaque in later films, indicating some excretion. Spontaneous urination had been noted previously.

Retrograde pyelography could not be performed in this male neonate for technical reasons. Urinalysis was negative; blood urea nitrogen 13 mg. per cent; white blood count, 7,600; neutrophils, 49 per cent; lymphocytes, 38 per cent; monocytes, 2 per cent; eosinophils, 7 per cent; basophils, 2 per cent; hemoglobin, 18 grams; hematocrit, 51 vol. per cent; and sedimentation rate, 1 mm. per hour (Wintrobe).

Clinical Course.—Because of the size of the mass and the vague possibility of a congenital neoplasm, surgery was performed on the sixth day of life. Through a left rectus incision a large multicystic left kidney was found, two separate groups of main vessels were ligated, and the mass was removed (Figs. 1 and 2). The right kidney, liver, pancreas, and other abdominal viscera were carefully examined and considered normal. The surgery and

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subsequent postoperative period were grossly uneventful. Transient melena on the first two days was attributed to an anal fissure.

Intravenous fluids, 50 c.c. of blood during surgery, and daily intramuscular penicillin and streptomycin constituted the medical therapy. Oral feedings were started on the third postoperative day and all were retained by the fourth day. Urination and defecation were normal.

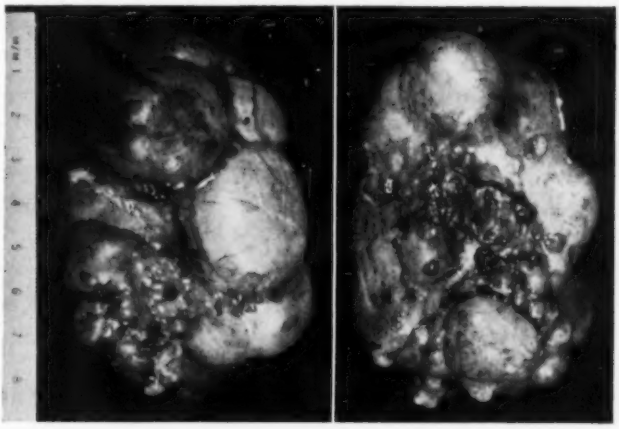

Fig. 1. Fig. 2.

Fig. 1.—Anterior view of multicystic kidney.
Fig. 2.—Medial view of kidney. The atretic ureter and blood vessels cannot be seen.

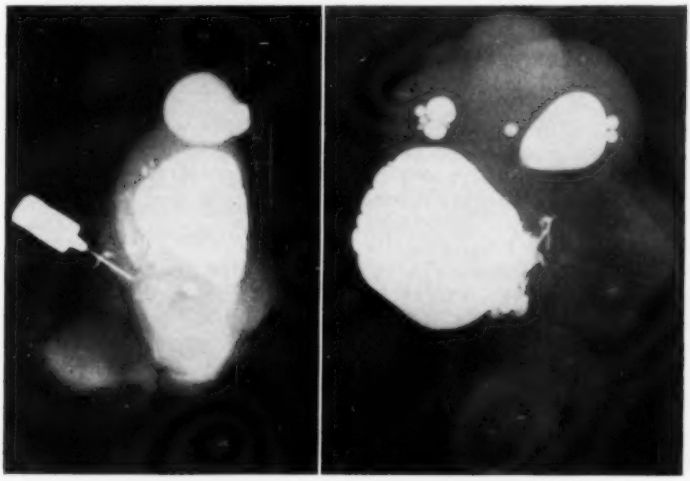

Fig. 3. Fig. 4.

Fig. 3.—X-ray of surgical specimen after the injection of Lipiodol into several cysts. The needle is in the atretic ureter but no dye could be forced into it. The pelvis could not be demonstrated by this technique.

Fig. 4.—X-ray of surgical specimen injected with Lipiodol, demonstrating the apparent lack of communication between many of the cystic structures. The needle had been inserted into several cysts and the specimen manipulated to facilitate spread of the dye.

The infant was discharged on the fourteenth day of life in excellent condition. Subsequent outpatient examinations have revealed normal growth and development. A normal intravenous right pyelogram was obtained on May 23, 1956.

Pathology.—

Gross: The specimen consisted of a multicystic mass resembling a kidney and measured 8 cm. from pole to pole, 5 cm. mediolaterally, and 3 cm. anteroposteriorly. On the medial surface there were fine filamentous structures which traced out to be renal artery, vein, and ureter. The specimen of ureter attached measured 1.5 cm. in length and 2 mm. in diameter. No lumen could be found in this structure grossly. The ureter communicated with an edematous gray, glistening area at the medial aspect of the parenchyma, but no true pelvis was encountered. Multiple sections through the mass revealed it to be composed of cysts ranging from 0.1 to 2.5 cm. in diameter. The cyst linings were smooth. The walls were opaque. Almost all of the cysts did not communicate with one another (Figs. 3 and 4). Some of the cyst linings had a brownish hue. Very little solid tissue was present between the cysts; for the most part, it was present at the peripheral portions of the mass. This tissue had a brown hue.

Microscopic: Multiple irregular cysts accompanied by only small quantities of renal parenchyma, which in many sites was hypoplastic in appearance. There were islands of tubules embedded in relatively large amounts of connective tissue stroma. The tubular epithelium was tall, except in those instances in which the tubules showed dilatation. These tubules also had flattened epithelium and were generally surrounded by less dense stroma. Hemorrhage was present in many areas of the sections.

The ureter was atretic but showed a microscopic lumen in several places.

Diagnosis: Multicystic kidney.

DISCUSSION

Congenital unilateral multicystic kidney disease is most likely a more common entity than the sparse reports in the literature would indicate. In most cases the markedly irregular outline of the mass would lead to a diagnosis other than hydronephrosis. Since the ureter is usually atretic or markedly narrowed, retrograde pyelography would almost invariably result in nonvisualization. There may be no ureteral orifice on cystoscopy, a finding which would argue against the presence of a congenital neoplasm. These findings would lead one to suspect a congenital cystic renal malformation.

The mass in the present case was discovered on the first day of life. This represents the first instance, to our knowledge, in which maternal rubella occurred during the first trimester of pregnancy. The etiology of this entity is unknown but it is apparently not a hereditary condition.

As has been previously suggested, there appear to be several rather distinct types of cystic kidneys:

1. *Multiloculated Cysts.*—In these cases a large segment of the kidney is intact and only a portion is replaced by large cysts, which are subdivided and partitioned to form lobules. A variant of this is the kidney containing multiple simple cysts.

2. *Polycystic Renal Disease.*—The organ shape and general calyceal pattern, though distorted, are relatively unchanged. Innumerable cysts of similar dimensions create a network which gives the kidney the appearance of a sponge. Microscopically many normal nephron structures are seen between the cysts. These cysts, and consequently the kidneys, are not usually large until later adult life. Such a diagnosis is rare in the neonate.

3. *Multicystic Kidney.*—In marked distinction to polycystic renal disease,

almost no normal parenchyma is visible either grossly or microscopically. The mass is composed of large cysts varying in both number and size, and there are often only remnants of the ureter or vessels. Usually no communication is demonstrable either between the cysts or between the pelvis, which is often rudimentary, and the cysts.

In the vast majority of cases these distinctions are evident both grossly and histologically. As Spence[1] has aptly pointed out: "More discriminating use of the descriptive terms 'multiocular,' 'multiple simple,' and 'multicystic' as applied in any given case will help unravel the problem of the cystic kidney."

Spence found fifteen cases in the previous medical literature and added four of his own. We would not entirely accept the last two of his cases though they may represent variants of the condition in the adult. Representative cases were also found in the works of Gross,[2] Higgins and associates,[3] and Campbell,[4] the latter two of whom state that such pathology should be differentiated from congenital polycystic disease.

It is possible that the rudimentary or absent ureter almost invariably accompanying the unilateral multicystic kidney may represent an essential differentiating point for those who may claim these cases as representatives of polycystic renal disease. In fifteen instances cited by Spence the ureter was atrophic or absent and in six cases no statement was made. Only in the cases of Wakely[5] and Schwartz[6] were the ureters said to be normal, though no orifice was seen during cystoscopy in the latter case. Generally the pelvis was either absent or rudimentary in most of the specimens adequately described. Since progressive metanephrogenic tissue organization will not take place in the absence of a ureteric bud,[7] it has been suggested that this may be the primary defect leading to subsequent cyst formation in the metanephros.[1, 8]

Whether the maternal rubella infection in the first trimester was etiologically related to the pathology is, of course, beyond our current knowledge. The association seems rather suggestive in view of the known adverse effects of this disease upon the developing fetus.

SUMMARY

A case of congenital unilateral multicystic kidney in a one-day-old neonate has been described. Maternal rubella was diagnosed at about 2 months' gestation.

It is emphasized that this entity is distinct from polycystic renal disease and, once the organ has been extirpated, one can anticipate a normally functioning contralateral kidney.

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DUODENAL COMPRESSION BY THE MESENTERIC ARTERY

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IT IS not difficult for the practitioner to diagnose bowel obstruction if it is complete, but considerably more diagnostic acumen is needed if the obstruction is partial, the complaints vague, and the symptoms not sharply defined. It is our purpose to present cases illustrating both categories, each caused by compression of the duodenum by the superior mesenteric artery.

Illustrative of the complete type is the following report of a case of acute obstruction in a premature infant.

CASE 1.—No abnormalities were noted on examination shortly after birth of a premature girl weighing 5 pounds 7 ounces. The infant was placed on a modified evaporated milk formula after twenty-four hours. Although the sucking reflex appeared strong, intake did not exceed one ounce. After the usual preliminary meconium stools, curds appeared, the stool being of the expected color and consistency.

On the morning of the third day, because of poor intake, she was given a tube feeding, which was promptly vomited. The vomited material contained bile, as did the stool. Throughout the day she continued to regurgitate both clear fluids and formula, in spite of a change to a low-fat formula and the addition of an antispasmodic.

Iodized oil introduced into the stomach passed readily into the duodenum. The duodenal bulb and the descending limb of the duodenum were dilated. The transverse portion was completely cut off at the level of the spine (Fig. 1). The opinion of the radiologist was that there was duodenal obstruction, probably due to mesenteric artery compression, since the obstruction occurred in the midline.

The infant, although premature, withstood surgery well. The duodenum was found obstructed at the expected point by an aberrant superior mesenteric artery and was relieved by duodenojejunostomy. The postoperative period was characterized by the ability of the infant to retain clear fluids but inability to retain milk. The infant was discovered to have a milk allergy, and the allergic symptoms were relieved by substitution of a soybean product. Now 18 months old, she has no intestinal symptoms referable to her former obstruction.

In contrast to the condition just described, we have the following case of an adolescent, who had a long history of digestive complaints, none sufficiently impressive to bring her to her physician.

CASE 2.—This 14-year-old girl first sought attention in 1940, when she came in with the complaint of midabdominal pain coming approximately fifteen minutes after meals and lasting an average of two hours. If it lasted until the next meal, the pain would be relieved for about fifteen minutes after taking food and then would return. She belched frequently and was constipated.

Throughout infancy she had had considerable vomiting, and for the past several years she had had intermittent

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abdominal pain and nausea, which were entirely relieved by vomiting. These episodes of abdominal pain and nausea occurred every month or two. She made the observation that she had vomited peas eaten several months before, a watermelon seed ingested six to eight months before, and corn eaten at least four months before.

Physical findings were not remarkable, but upon attempting barium studies of the stomach, there was so much food present that the patient was instructed to return the next morning, after omitting breakfast. Visualization then revealed that the duodenum was dilated to about three

Fig. 1.

or more times the ordinary diameter, the dilatation stopping at approximately the location of the jejunal junction (Fig. 2). Partial obstruction was obvious.

A few days later it was revealed during surgery that this partial obstruction of the small bowel was caused by the pull of the superior mesenteric artery where it crossed the duodenum. After the obstruction was relieved by duodenojejunostomy, the patient gained twelve pounds in three months, was relieved of constipation, and did not have attacks of vomiting, although x-ray studies failed to show any return of the duodenum to normal size.

At the age of 22 and married, she returned with a complaint of upper abdominal, gnawing pain radiating to the back and present on arising for two or three weeks. Nausea had been present for two to three days but no vomiting. She was belching freely, but there were no stool abnormalities, and her weight was constant at 92 pounds.

Fig. 2.

X-ray studies revealed a slightly dilated stomach which contained excess secretion and food particles. The duodenum to the level of the midline was dilated about three times normal and also contained food particles. It was not possible to demonstrate a functioning duodenojejunostomy, but a five-hour emptying film showed one-half of the barium had reached the cecum, while the residue remained in the stomach and duodenum. The impression was that of duodenal ileus with gastric retention.

She was given a trial of neostigmine bromide and instructed to assume the knee-chest position for fifteen minutes after meals. On this regimen she had no further abdominal pain and for two and one-half years had only minor complaints, even when the medication was stopped. There was no difficulty during pregnancy and labor, and her weight was stable at 104 pounds.

Repeat x-ray studies showed little or no change in the status of her duodenal ileus. This young woman was last seen in May, 1952, prior to leaving the state.

COMMENT

Although no attempt will be made to give a full bibliography on the subject of duodenal obstruction by pressure from a mesenteric artery, the condition is rarely mentioned in the literature. Hertz[2] defines the condition as one in which there is a compression of the duodenum produced by pressure between the vertebrae and the aorta on the one side and the root of the mesentery containing the superior mesenteric artery on the other. Since the duodenum is normally slightly narrowed under the root of the mesentery, any further compression tends to cause obstruction.

Cuna and Day[1] mention weight changes as a frequent prelude to the appearance of distress. The process of dieting, especially if drastic, may cause the fat deposits in the intra-abdominal mesenteries, omenta, and retroperitoneal spaces to shrink to the point where anatomical lines are changed due to angles and stresses. Conversely, the addition of fat may cause the same type of distortion. Where these stresses have been in operation over a long period of time, as in our second case, stasis leads to inertia of smooth muscle, with resulting extensive duodenal dilatation. Weight change has not been a factor in our cases.

As would be expected, total obstruction would be more likely to be found in a newborn infant, while those who manage to survive this period, with less acute compression, and have reached older age groups are those who have chronic complaints of "gas pains" and indigestion. Considering the millions of dollars spent annually on pills, powders, and physicians for those seeking relief from distention and dyspepsia, mechanical obstruction should be considered as a cause closely after ulcer and gall bladder pathology.

Upper gastrointestinal fluoroscopic and x-ray studies are necessary to make a diagnosis. Unfortunately, the roentgenologist and the clinician are too often unaware of this condition, and reverse peristalsis in the duodenum is ignored. Surging in a slightly dilated duodenum, especially if accompanied by reluctance of the barium column to enter the jejunum, should warrant the diagnosis of duodenal ileus. The extent of this condition and whether it is functional or organic can be studied further by films taken in numerous positions, including the horizontal, oblique, and prone. In some instances the patient must be placed in the knee-chest position to relieve the obstruction.

Medical management is sufficient in the less acute cases, although drugs have not given apparent relief. After the fluoroscopic studies the roentgenologist often is able to suggest the most beneficial position to favor emptying; but, where obstruction is complete or essentially so, duodenojejunostomy is performed.

SUMMARY

In the presence of the triad of belching, bloating, and borborygmus, especially if accompanied by midepigastric discomfort, vomiting, and constipation, and if symptoms are chronic and recurring, compression of the duodenum by the superior mesenteric artery must be considered. Two cases are reported, one in a premature newborn infant, where total obstruction was present, and one in a 14-year-old girl, where distress had been present from birth. Management is suggested. The condition may be less rare than previously assumed and, if there are long-standing complaints of dyspepsia, this condition should be ruled out.

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An Inquiry Into the Cause and Cure of the Cholera Infantum

. . . It seldom appears in Philadelphia till the middle of June, or the beginning of July, and generally continues till near the middle of September. Its frequency and danger are always in proportion to the heat of the weather. It affects children from the first or second week after their birth, till they are two years old. It sometimes begins with a diarrhea, which continues for several days without any other symptom of indisposition; but it more frequently comes on with a violent vomiting and purging, and a high fever. The matter discharged from the stomach and bowels is generally yellow or green, but the stools are sometimes slimy and bloody, without any tincture of bile. In some instances they are nearly as limpid as water. Worms are frequently discharged in each kind of the stools that has been described. The children, in this stage of the disease, appear to suffer a good deal of pain. They draw up their feet, and are never easy in one posture. The pulse is quick and weak. The head is unusually warm, while the extremities retain their natural heat, or incline to be cold. The fever is of the remitting kind, and discovers evident exacerbations, especially in the evenings. The disease affects the head so much, as in some instances to produce symptoms not only of delirium, but of mania, insomuch that the children throw their heads backwards and forwards, and sometimes make attempts to scratch, and to bite their parents, nurses, and even themselves. A swelling frequently occurs in the abdomen, and in the face and limbs. An intense thirst attends every stage of the disease. The eyes appear languid and hollow, and the children generally sleep with them half closed. Such is the insensibility of the system in some instances in this disease, that flies have been seen to alight upon the eyes when open, without exciting a motion in the eyelids to remove them. Sometimes the vomiting continues without the purging, but more generally the purging continues without the vomiting, through the whole course of the disease. The stools are frequently large, and extremely fetid, but in some instances they are without smell, and resemble drinks and aliments which have been taken into the body. The disease is sometimes fatal in a few days.

BENJAMIN RUSH, *1773.*

Clinical Pathological Conference

CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

CLINICAL HISTORY

AT AGE 2 years, this patient developed nocturnal fever and pain in the neck and shoulders. Within a month the left elbow became hot, tender, and swollen, and over the next six months nearly all the joints, including the fingers, became similarly involved while the predominantly nocturnal fever continued. Treatment during this period consisted of bed rest, penicillin, "heart pills," and vitamin B_{12}. The intermittent fever continued for two years, leaving the joints stiff and preventing her from walking.

Two weeks before she was admitted to another hospital, and after an upper respiratory infection occurred in her father and a sibling, the patient developed a sore throat, fever, malaise, and generalized abdominal pain. The family physician found a mild pharyngitis and otitis media and prescribed penicillin. However, two days later, he found some dullness of the left lung posteriorly and prescribed chlortetracycline. Despite this, the temperature rose to 105.6° F. Cortisone, 50 mg. every six hours, was administered, but the temperature continued to spike. Over the period of that hospitalization (prior to entering The Children's Medical Center) there developed apical systolic and diastolic murmurs, progressive splenomegaly, and a falling peripheral leukocyte count. At the time of transfer to this hospital, the patient was receiving 100 mg. of cortisone daily.

The family history revealed that the father had rheumatic fever as a child but recovered without any rheumatic stigmas.

On admission to The Children's Medical Center, the patient's temperature was 104° F., the pulse 156 per minute, respirations 28 per minute, and the blood pressure 110 mm. Hg systolic, and 56 mm. diastolic. She was a pallid, acutely and chronically ill girl, complaining of pain in the neck, elbows, knees, and fingers, and, to a less degree, in the hips and wrists. Movement of the chest in respiration was limited. There was bleeding from the gums, a few cutaneous petechiae, and oozing with ecchymosis at the sites of needle punctures. The heart was minimally enlarged, with a high-pitched grade II apical systolic murmur and a questionable apical grade I diastolic rumble. The lungs were clear. The spleen could not be felt because of gaseous distention, but the liver was palpable 3 cm. below the costal margin.

At the time of admission, examination of the urine showed a pH of 4.5, a specific gravity of 1.019, albumin 100 mg. per cent, and a few erythrocytes in the sediment. The blood examination revealed 7.4 grams per cent of hemoglobin, a leukocyte count of 4,000 per cubic millimeter with a differential of 9 per cent polymorphonuclears, 3 per cent band forms, 7 per cent "immature" forms, 66 per cent lymphocytes, and 14 per cent monocytes. The platelets numbered 11,000 per cubic millimeter. The prothrombin activity was 13 to 19 per cent of normal. The "accelerator globulin" was 44 per cent of normal. An aspiration of the bone marrow revealed a striking arrest of myeloid and erythroid elements; lymphocytes were present in all stages of development and predominated in numbers. Megakaryocytes were present but were slightly immature. The bleeding time was 20 minutes; the clotting time was one hour. The stool guaiac was 2 plus. A single blood culture was negative.

The admission roentgenograms showed the lungs to be clear, the heart to be normal in contour but top-normal in size. The small bowel was moderately distended; the colon was poorly visualized. The long bones appeared delicate and overtubulated. The joints showed loss of articular cartilage and an irregular loss by erosion of secondary ossification centers.

The patient was started on cortisone, 25 mg. every six hours; this was raised to 50 mg. every six hours the next day, supplemented by oxytetracycline 200 mg. every six hours. Despite this, and alcohol sponges, the temperature ranged from 101.4° to 104° F. throughout the hospital stay.

The patient continued anorexic, lethargic, and continued to ooze blood from needle puncture sites and from the gums. On the third day she started to have grossly bloody stools. Administration of vitamin K oxide, 50 mg., vitamin C, and whole transfusions daily did not alter the picture. On the third day slight jaundice developed and some hematuria. On the fourth day she developed a macular rash all over the body which faded with pressure. While being turned on her back, she suddenly ceased to breathe.

DISCUSSION

DR. JONATHAN COHEN.*—The patient was a female; most juvenile rheumastoid arthritis occurs in female in the period from age 2 to 4 years. In two large series[1, 2] of about sixty cases each, 40 and 37 per cent occurred in that period of life. The fact that "heart pills" were given during the early stages of this child's illness suggests that she was probably thought to have some heart involvement. In the typical rheumatoid arthritis, the heart involvement consists principally of pericarditis, with a few cases showing a nonspecific valvulitis, and still fewer, myocardial involvement at postmortem. Some patients will show electrocardiographic changes with rheumatoid activity, but these are transitory, consisting primarily of a split QST, or a tachycardia, and at post mortem, little change is found in the myocardium.

We then come to the present illness, which began with an upper respiratory infection. The high temperature is

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not characteristic of Still's disease at this stage. They usually have intermittent episodes of low-grade fever. Here, the fever was not intermittent but spiking, and it continued well elevated during the hospital stay. Still's disease, as described by him in 1897,[3] occurred in children under 5 years with atrophic arthritis, and was accompanied by lymphadenopathy, splenomegaly, and a leukocytosis. Since leukocytosis is not always a feature of cases of chronic atrophic arthritis in the pediatric age group, the tendency now is to discard the eponym and use the term "juvenile rheumatoid arthritis." Still's series included three post mortems without microscopic data. Mortality in juvenile rheumatoid arthritis is usually low, under 4 per cent, although in one series from Great Ormond Street it rose to 20 per cent. In the two-dozen-odd published postmortem reports of cases of juvenile rheumatoid arthritis, a large percentage of the patients died with amyloid disease, some with the nephrotic syndrome and uremia secondary to the amyloid disease. Amyloid has been reported in juvenile rheumatoid arthritis to involve both the liver and kidney. Dr. Marian Ropes at the Massachusetts General Hospital says that about 10 to 15 per cent of her rheumatoid patients have some amyloid disease, and that 50 per cent of these patients have increased Congo red retention—up to 20 per cent above normal.

In the present case the signs of either kidney or liver disease are indeed not marked. A slight albuminuria, a decrease in prothrombin activity and in A-C globulin are the only indications of either renal or hepatic injury. Amyloid disease involving the liver would usually give a much larger liver than is recorded in the protocol.

The coexistence, I think, of this very unusual blood picture and rheumatoid arthritis should lead to speculation. When the blood platelets number 11,000 per cubic millimeter and an agranulocytosis is present, one immediately thinks of leukemia. Acute leukemia cannot be ruled out in this case, although statistically it is unlikely. I feel that infection is the most likely cause of this girl's death, although no focus of localization was evident. The single blood culture was negative, but one negative blood culture does not rule out a bacteremia. Cortisone may have obscured many of the symptoms of infection, and attention should be called to the generalized abdominal pain which the patient suffered. We have had a patient with leukemia and with minimal abdominal pain in whom the symptoms of a ruptured appendix, which later developed, were obscured by cortisone.

Dr. Wittenborg, may we see the pertinent films?

DR. MARTIN H. WITTENBORG.—The heart, you can see, is slightly enlarged in transverse diameter, but the configuration is not specifically abnormal. The bones of the upper and lower limbs are overtubulated and frail looking. The secondary ossification centers are irregularly trabeculated. Such changes are uniform in all areas but are quite nonspecific. In the hip joints the cartilaginous spaces are a little bit narrow.

DR. COHEN.—Can you judge the spleen size?

DR. WITTENBORG.—We just could not be certain whether the spleen was enlarged or not. I would expect that it was not massively enlarged or we would have displacement of the bowels.

DR. COHEN.—The x-rays show us, then, that the changes of rheumatoid arthritis in the growth centers and in the joints themselves are quite evident, but no information is given concerning the final episode; in particular, there are no findings indicative of an acute infection, that is, an osteomyelitis or an inflammatory process in the lungs. I think the protocol is quite clear that she had enlargement of the liver and perhaps the spleen. The observation that the main post-mortem findings in atrophic arthritis generally indicate some disease of the liver would lead me to feel that at least part of her difficultly lies in that organ.

There are two other things that I would like to mention. One of these is the possibility of drug-induced aplastic anemia, and in a rheumatoid a good possibility is that she received gold, which is an established cause of liver damage, or that chloramphenicol induced an aplastic anemia. I am, therefore, left with the diagnosis of rheumatoid arthritis with a complication of aplastic anemia. I feel that the aplastic anemia may well have been due to an infection, and the organism of this infection is a matter of speculation. I feel that post-mortem examination, incidentally, will show pericardial and perhaps also pleural and peritoneal adhesions, which have been seen in very many of these cases.

DR. CRAIG.—Dr. Hartman might like to tell us what this level of A-C globulin means in such a patient in the presence of aplastic anemia and perhaps in the presence of suggested severe infection.

DR. JOHN HARTMAN.—I think that this patient presented distinct hematologic findings: one was the gradual drop in the white count, platelets, and hemoglobin, which occurred in the two weeks prior to her death. The hematology group saw the child the day before death because of the abnormal peripheral blood. A bone marrow aspiration smear was consistent with a hypocellular marrow. A study of the coagulation defect revealed that her clotting time and her bleeding time were markedly prolonged. We felt that the bleeding time was prolonged because of her low platelet count. Her clotting time should not have been that prolonged, even with a platelet count count of 11,000 per cubic millimeter. There was a markedly diminished prothrombin content which could be due either to a defect of absorption of vitamin K, or, more likely, to an intrinsic disease of the liver. The low A-C globulin is within the range found only with severe liver disease. Another test, which was not on the protocol, indicated that she had a markedly high antithrombin level, which means that there is some substance in the blood which counteracts the action of thrombin. High antithrombin levels likewise have recently been reported in liver disease. We were unable to help her either by giving her fresh blood, which would contain A-C globulin and perhaps platelets, or by giving her vitamin K, which we wish to emphasize was given empirically.

DR. CHARLES A. JANEWAY.—I do not see how anybody can do anything but

speculate about this fascinating problem. Whatever this was, it developed after an infection that at least had some of the characteristics of a streptococcal infection. In rheumatoid arthritis, it is pretty clear that although it does not have anything like as definite a relation to hemolytic streptococcus infection as rheumatic fever, a fair percentage of cases of rheumatic arthritis do arise after hemolytic streptococcal disease, particularly in childhood.

Did the child just have an overwhelming recurrence of rheumatoid arthritis? The hematologic picture does not fit anything we have seen. We have seen acquired hemolytic anemia in rheumatoid arthritis in a number of cases. Felty[4] described a syndrome some years ago of high spiking fever, joint symptoms, a large spleen, and leukopenia. While I was at Hopkins, I looked up the three cases on which he based his article. I came away with the opinion that the three patients did indeed show big spleens, leukopenia, and rheumatoid arthritis, but the group did not really constitute a syndrome. A large spleen may develop in rheumatoid arthritis, which may trap blood in the circulation and tend to lower platelets and leukocytes.

DR. CRAIG.—He did not say anything about the bone marrow?

DR. JANEWAY.—No, they did not look at bone marrow in those days.

The patient under discussion today developed a rash on the last day of life. This could be considered a manifestation of rheumatoid arthritis as could the high temperature. I would disagree with Dr. Cohen about this. I believe we have been inaptly applying the term Still's disease to cases of acute rheumatoid arthritis, in which the one salient characteristic is a high swinging temperature, which is almost invariably associated with marked leukocytosis and rash. This patient's blood did not react in that way.

The hematologic picture is very difficult to understand. The only possibilities, if you try to put this all together, seem to be that Dr. Cohen, by citing the literature, and Dr. Hartman, by his coagulation studies, between them have made a pretty strong case for hepatic disease—but then what kind of hepatic disease? Is this severe amyloidosis? If it is, I would take issue with Dr. Cohen and say that it pretty well spared the kidney because 100 mg. per cent of albumin is only five times the normal concentration. I do not know what kind of hepatic disease this is. This could hardly be a virulent attack of infectious hepatitis, for example, which might cause leukopenia, but not aplastic anemia. It could cause the coagulation effects, but the patient should have had more jaundice. Did this patient have severe bacterial endocarditis? In this individual with a heart lesion, the spiking fever and petechiae might be signs of bacterial endocarditis, but the negative blood culture is against this. Rheumatoid arthritis disturbs the serum proteins very markedly and is one of the prime causes of hypergammaglobulinemia. Now, we do not know what those gammaglobulins are and what they are doing. They are presumably a tremendous response on the part of the lymphoid system, yet nobody has ever demonstrated directly that they represent antibodies to any known agent.

DR. C. D. COOK.—I can not disagree with Dr. Cohen's diagnosis here, but one thing puzzles me. This is a child who supposedly had rheumatoid arthritis for two years, yet we do not have a typical fusiform swelling of the hands of a child with rheumatoid arthritis. I would consider the diagnosis of lupus erythematosis. I think many of the signs could be explained on this basis. The joint pains of several years' duration, the macular rash, the leukopenia, the anemia, the thrombocytopenia—are all consistent with lupus erythematosis. This child did not have the characteristic renal findings but I think 10 to 15 per cent of children with lupus have only a minimal renal involvement.

DR. JANEWAY.—Dr. Cook, you reviewed all our cases here. What age is the youngest child in that series?

DR. COOK.—I believe that our youngest child was, at the onset of the disease, either 2½ or 3 years old, although the more typical age is certainly closer to 7 to 9.

DR. NICHOLAS STAHL.—I saw this child because of bleeding from the rectum, and this raised surgical problems which I did not solve. I was helped by the fact that when I saw the child, she was still bleeding from a needle puncture that had been done an hour before, which seemed to obviate any corrective surgery, even if it were necessary.

DR. CRAIG.—Dr. Stahl, did this patient have acute joint symptoms at the time of admission? The protocol is not clear as to whether or not there were any.

DR. STAHL.—She was a very apprehensive and irritable child and had a tremendous amount of pain, but it seemed to me polyarticular in nature.

DR. PRYLES.—I should like to mention a case pointed out about a week or two ago at the City Hospital. This was a boy who was treated for subacute bacterial endocarditis on penicillin over a long period of time. He finally developed an arthritis and at the same time had other evidences of an immunovascular disease, characterized by anemia, agranulocytosis, and thrombocytopenia.

DR. CRAIG.—At autopsy this girl had severe rheumatoid involvement, by external examination of her knees, wrists, and fingers, with shiny skin, fusiform swelling, and limitation of motion in the affected joints. This was confirmed by direct pathologic examination of her left hip and the right shoulder joint. In both those joints there was a severely destructive lesion with numerous deep erosions and replacement of the cartilaginous articular surfaces (Figs. 1, 2, and 3) by pannus formation. The bony trabeculae displayed a marked osteoporosis, as was predicted by the roentgen examinations. The bone marrow (Fig. 4) was marked by hypoplasia, with a decrease in both erythroid and myeloid forms, but an adequate number of megakaryocytes. A few lymphocytes were also recognized in the marrow. In spite of the hypocellular nature of the marrow, it contained a few adult lipid cells, but rather a gelatinous matrix which suggested a fairly sudden alteration to a hypoplastic state. No evidence of leukemia was present. The spleen, though three times the normal weight, also showed a marked depletion of both the red and white pulp with considerable congestion of

the sinusoids (Fig. 5). Other pathologic features which were probably related to the rheumatoid state included a fibrous pleuritis and a pericarditis.

The immediate cause of death was an overwhelming sepsis, caused by the organism *Colibacterium coli*, which was found by culture at post mortem to be present in the heart's blood, the

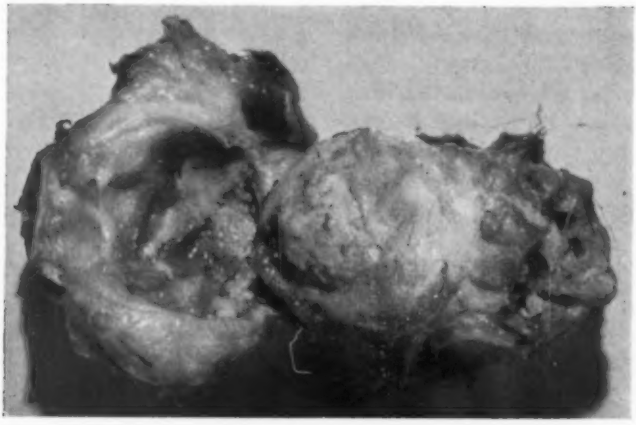

Fig. 1.—The head of the femur and acetabulum have been removed and opened. There is marked destruction of the articular cartilage and pannus formation.

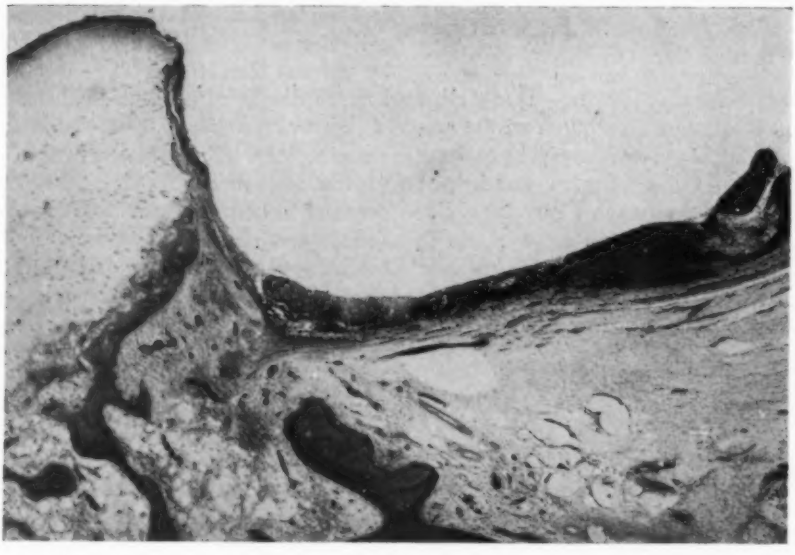

Fig. 2.—Head of humerus. A deep ulceration is present in the articular cartilage, with a base of granulation tissue. (Hematoxylin and eosin; ×25; reduced 1/12.)

Fig. 3.

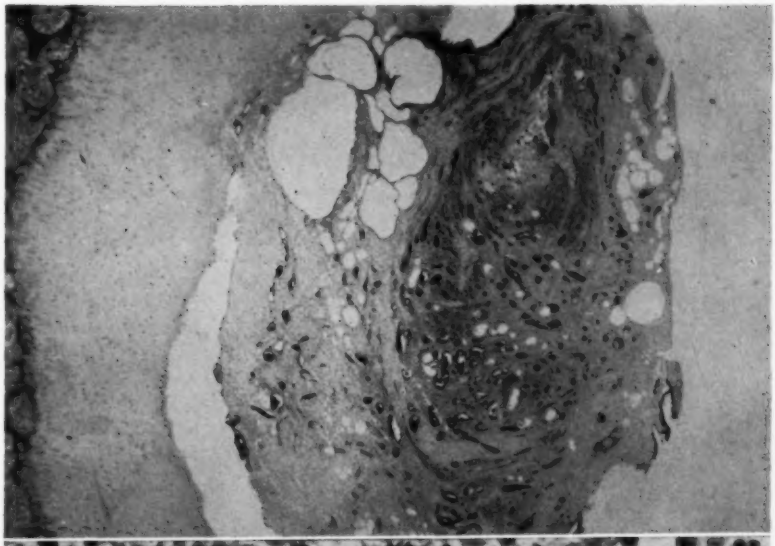

Fig. 4.

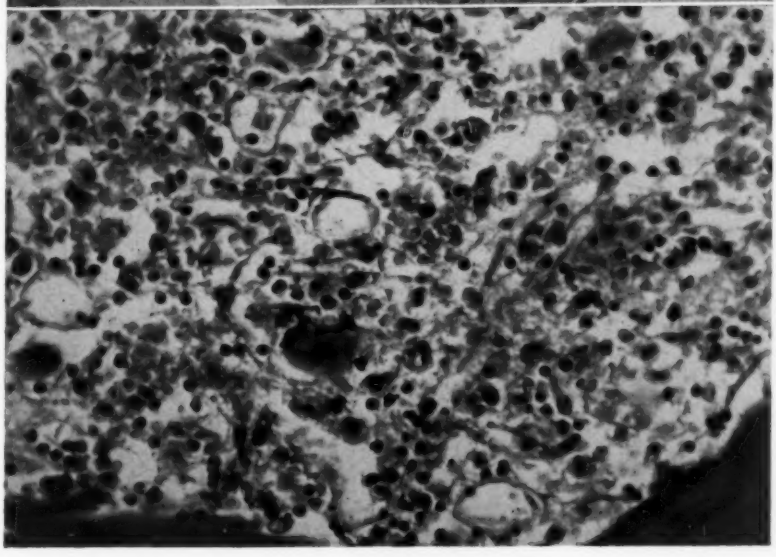

Fig. 3.—Acetabulum. Pannus formation is present on the articular surface. (Hematoxylin and eosin; ×35; reduced 1/12.)

Fig. 4.—Bone marrow. Marked depletion of the marrow is present with a myxomatous stroma. Lymphocytes, macrophages, and structural cells are the principal forms seen. (Hematoxylin and eosin; ×200; reduced 1/12.)

Fig. 5. Fig. 6.

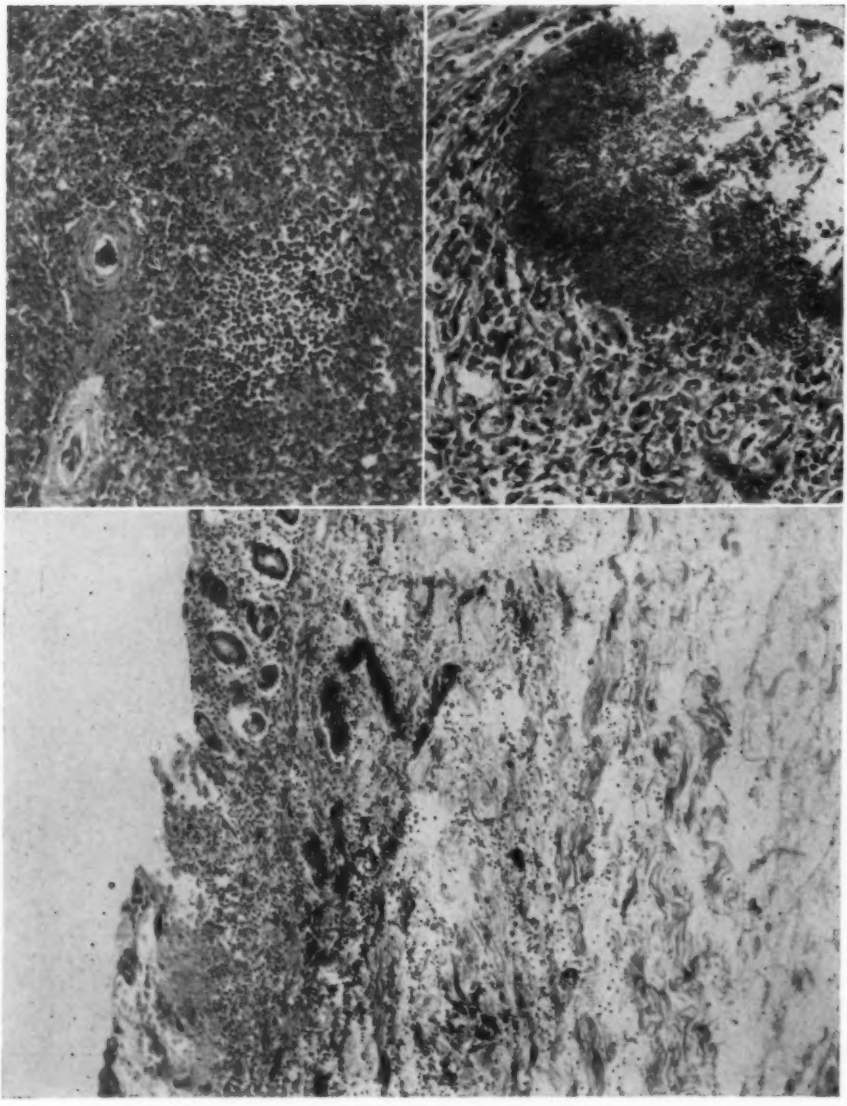

Fig. 7.

Fig. 5.—Spleen. Marked depletion of the white and red pulp is present. (Photomicrograph: ×150.)

Fig. 6.—Stomach. Many yeast forms of Candida are present in the ulcer of the mucosal surface. (Hematoxylin and eosin: ×125.)

Fig. 7.—Large intestine. There is marked edema of the submucosa with a scant mononuclear infiltration. An erosion of the mucosa is present. (Hematoxylin and eosin: ×135.)

lung, the middle ears, and the pleural and pericardial fluid. The source of this infection appeared to lay in the gastrointestinal tract. In both esophagus and stomach there were gross ulcers with invasion of the submucosa by monilial and bacterial forms (Fig. 6). In the large bowel, similar foci of mucosal necrosis with heavy bacterial invasion of the outer layers of the intestinal wall were found (Fig. 7). lesion. It is difficult to relate it to either the coliform sepsis or the rheumatoid state.

Evidence of cardiac failure was present, however, because of the finding of free fluid in the peritoneal cavity (300 c.c.), pleural cavities (3,800 c.c.), and pulmonary edema on microscopic examination.

The liver, in spite of the patient's jaundice, showed only a mild peri-

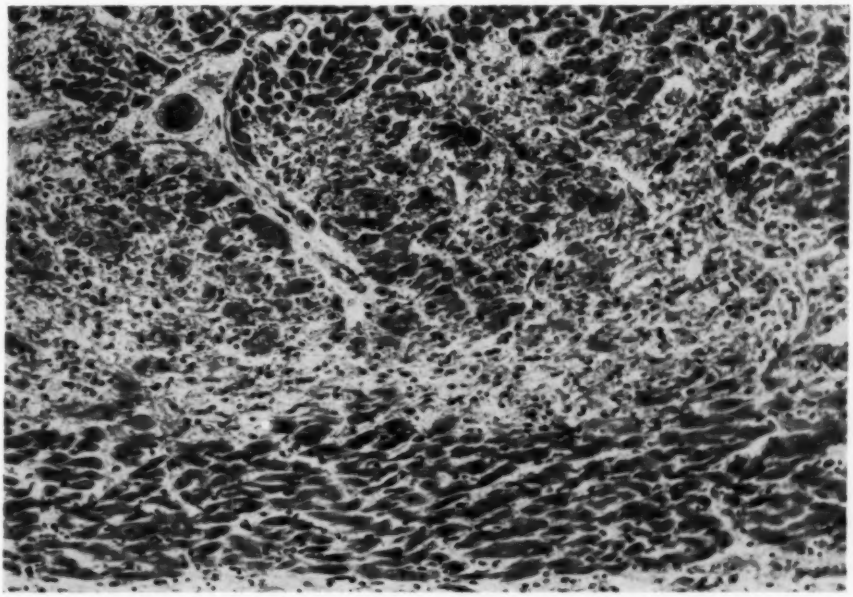

Fig. 8.—Heart. The areas of recent myocardial necroses are present in the subepicardial regions of the heart. (Hematoxylin and eosin; ×150.)

In none of these areas were there inflammatory cells in any numbers, undoubtedly a reflection of the hypoplastic bone marrow and agranulocytic state of the peripheral blood. In the section of the left ventricle of the heart, just beneath the epicardium was a band of recent myocardial necrosis, accompanied by an increased number of mononuclear cells (Fig. 8). We found no bacteria associated with this portal inflammation. The jaundice must be ascribed to toxic effects of the sepsis and to destruction of red blood cells. Anatomic evidence for the latter is present in the erythrophagocytosis in the liver, spleen, and bone marrow. The bleeding tendency, displayed in the pelvic hemorrhage in the kidney, the skin petechiae, and the blood-tinged fluid collections in the major body cavities may in part be due

to the sepsis, the toxic effects on capillary walls, and to the lowered platelet count.

In summary, then, we have a patient with severe chronic rheumatoid arthritis and an aplastic anemia, in whom there developed gross ulceration and invasion of the intestinal wall with monilia and bacteria, leading to generalized sepsis, cardiac failure, and death.

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Medical Progress

SUICIDE IN CHILDREN AND ADOLESCENTS

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SUICIDE ranks fifth in frequency as a cause of death among young people 15 to 19 years of age (Table I). It is surpassed in this age group only by accidents, malignant neoplasms, rheumatic heart disease, and homicide, principally in Negro children. In 1954, the last year in the United States for which figures are available, 261 adolescents lost their lives in this way—more than the number that died from renal disease, pneumonia, tuberculosis, leukemia, or poliomyelitis. Suicide accounted for 2.5 per cent of all deaths in this age group in 1954 in the United States.

In a recent report from Yale for the years 1925-1955[1] suicide was the second most frequent cause of death among students. It accounted for 12 per cent of all deaths. Moreover suicide was the only major cause for which more deaths occurred than was expected, the general death rate among Yale students being considerably lower than in the general population. In an earlier study (1925-1935) made in various colleges, suicide was the third most frequent cause of death.[2]

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Even in the 10- to 14-year-old children the death rate from suicide is not inconsiderable. Each year from thirty-five to sixty children take their own lives. Suicide accounted for 0.59 per cent of all deaths in this age range in 1954 in the United States. The number of deaths (see Table II) is comparable in magnitude to the number of children dying from appendicitis, tuberculosis, homicide, diabetes, or meningococcus disease.

It is important to keep in mind that the number of deaths from suicide is probably considerably greater than is given in the mortality data. Ordinarily every effort is made to conceal a suicide death and to attribute it to accident or other cause, thereby shielding the parents from the shame and guilt feelings associated with a self-inflicted death. Some of the motor vehicle accidents in young people due to reckless driving may have in them a suicidal component. Neavles and Winokur,[3] in a psychiatric study of more than thirty hot rodders, concluded that there is a great self-destructive element in their behavior. "These boys," they wrote, "gamble with their lives."

In vital statistics reports deaths from suicide and homicide are customarily included under "accidents,"

along with motor vehicle accidents, mishaps with firearms, drownings, and so on. In suicide and homicide, however, there is an element of conscious intention which is not present in other "accidents." For this reason it seems justifiable to consider them separately from other accidental deaths.

The relative importance of the suicide problem in children and adolescents has increased as other causes of death, notably the infections, have diminished. Nevertheless the recent literature contains little on this subject. The only important contributions are the report on suicide attempts in children by Bender and Schilder[4] in 1937, which has been further amplified by Bender[5] in 1953, a report by Stearns[6] of an interesting group of boys who hung themselves, a study by Schaehter and Cotte,[7] and an excellent account of childhood suicide in England by Mulcock.[8] By contrast a large number of extensive studies appeared in the last century and during the early years of this century. Notable among these were the contributions of Morselli,[9] Durand-Fardel,[10] Périer,[11] Siegert,[12] Baer,[13] and Redlich and Lazar.[14] We have found nothing on this subject in the pediatric literature except for the report of a suicide attempt in an 11-year-old boy in the *Archiv für Kinderheilkunde*.[15] The principal contributions have been made by sociologists and psychiatrists.

There was ample reason for concern about suicide in children and adolescents during the latter half of the nineteenth century and the early years of the present century. The rates were exceedingly high, especially in Prussia, France, and Russia. Moreover, they were rising.

About as many children and adolescents died from suicide each year in

TABLE I. THE NUMBER OF DEATHS FROM SELECTED CAUSES, UNITED STATES, 1954, 15 TO 19 YEARS

All causes	10,302
Accidents, poisonings, and violence (including suicide and homicide)	5,450
Malignant neoplasms (including leukemia and lymphosarcoma)	830
Rheumatic heart disease[1]	464
Homicide	400
Suicide	261
Nephritis and nephrosis	244
Leukemia	235
Pneumonia, all forms[2]	226
Congenital malformations	206
Tuberculosis, all forms[3]	166
Complications of pregnancy	159
Vascular lesions of central nervous system	155
Poliomyelitis[4]	123
Diabetes	92
Appendicitis	58

Source: Vital Statistics of the United States, 1954, vol. II, Table 50.

[1]Sixth Revision of the International Lists, Nos. 410-443.

[2]Sixth Revision of the International Lists, Nos. 490-493.

[3]Sixth Revision of the International Lists, Nos. 001-019.

[4]Sixth Revision of the International Lists, Nos. 080-081.

TABLE II. THE NUMBER OF DEATHS FROM SELECTED CAUSES, UNITED STATES, 1954, 10 TO 14 YEARS

All causes	6,273
Accidents (including suicide and homicide)	2,732
Malignant neoplasms (including leukemia and lymphosarcoma)	781
Leukemia	310
Congenital malformations	271
Pneumonia, all forms	219
Rheumatic fever	204
Acute poliomyelitis	161
Rheumatic heart disease[1]	150
Nephritis and nephrosis	150
Vascular lesions of central nervous system	113
Homicide	93
Benign and unspecified neoplasms	87
Diabetes	75
Appendicitis	74
Nonmeningococcus meningitis	51
Anemias	45
Meningococcal infections	40
Suicide	37
Tuberculosis, all forms	35

Source: Vital Statistics of the United States, 1954, vol. II, Table 50.

[1]Sixth Revision of the International Lists, Nos. 410-443.

Prussia during the thirty-year period 1869-1898 as in the whole of the United States today (Table III). In the five-year period 1903-1907, the suicide rates in Saxony for children 10 to 14 years of age were 5.3 per 100,000 in males and 2.6 in females; in the 15- to 19-year-old group the figures were 34.1 for males and 19.2 for females.[16] These rates are almost ten times as high as the comparable all suicides took place in children 10 to 14 years old. On the other hand, in Westphalia and the Rhineland, both of which are mainly Catholic, the rates, though still much higher than are current today, were only a fraction of those in the above-named provinces (Westphalia, 2.5 per cent; Rhineland, 4.8 per cent).

The number of suicides in children under 15 rose steadily in Prussia,

TABLE III. COMPARISON OF THE MEAN ANNUAL NUMBER OF DEATHS FROM SUICIDE IN THE PRUSSIAN KINGDOM, 1869-1898 (BAER), AND THE NUMBER OF DEATHS FROM SUICIDE IN THE UNITED STATES, 1954

AGE (YR.)	PRUSSIA			UNITED STATES 1954		
	TOTAL	MALES	FEMALES	TOTAL	MALES	FEMALES
0-9	3.1	2.4	0.7	0	0	0
10-14	53.8	42.5	11.3	37	30	7
15-19	328.1	221.8	106.3	261	191	70

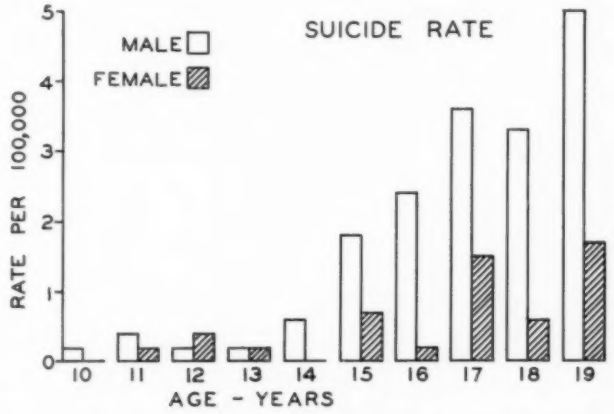

Fig. 1.—Average annual death rates per 100,000 from suicide in white persons aged 10 to 19 years, 1953-1955. (Industrial Policyholders, Metropolitan Life Insurance Company. Data kindly supplied by Dr. George Wheatly.)

United States figures for 1954. Even in children under 10 years of age the average number of suicide deaths each year during the thirty-year period 1869-1898 in Prussia was 3.1.

Within Prussia itself the rates varied widely. They were especially high in Saxony, Silesia, and Brandenburg. In Saxony over 12 per cent of from an annual average of 38.2 in 1869-1873 to 64.8 in 1894-1898. At the same time the total number of suicides at all ages rose from 2,929 to 6,431 per year. Germany maintained high rates of childhood and teenage suicides up to World War II.

In France, too, the number of suicides in children and young people

was 61 and 303, respectively, in 1881 and rose to 90 and 450 by 1895.[13]

The rates among children in certain parts of Russia were also very high during the early years of this century. Serkoff[17] reports that 4.5 per cent of all suicides in Moscow during the years 1908-1909 were in the age group 8 to 14 years, and 38.1 per cent were in the 15- to 20-year-old group. The corresponding figures for the United States in 1954 were: 10 to 14 years, 0.23 per cent, and 15 to 19 years, 1.6 per cent. Recent figures for suicide in Russia are not available, vital statistics being a state secret there.

The incidence of suicide by age is shown in Figs. 1 and 2. Self-destruction is rare under 10 years and remains infrequent until about 15 years of age, when a sharp rise in both boys and girls takes place. The rate continues to increase in boys throughout

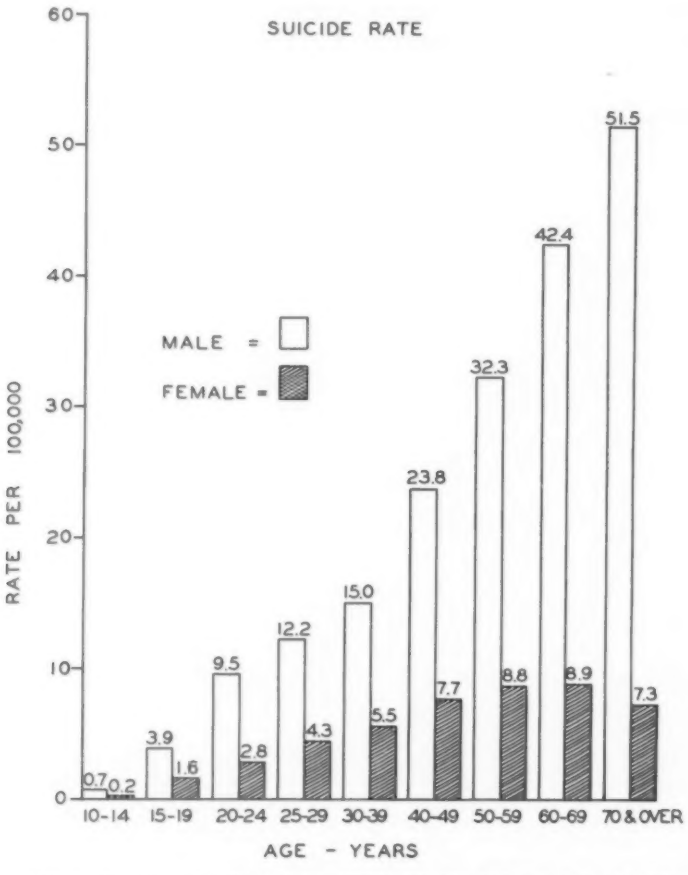

Fig. 2.—The death rate per 100,000 from suicide by age and sex, United States, 1954.

the 15- to 19-year age period; the rate for the girls shows an upward trend during these years.

After the adolescent years, the suicide rate in males climbs steadily and is highest in the aged (Fig. 2). There is a rise in females also but it is more gradual and the rate is actually lower in the decades 70 and over than in the preceding three decades.

15 TO 19 YEARS OF AGE

The mortality rates from suicide in a selected group of countries for young people 15 to 19 years of age are shown in Table IV. The median male death rate is 6.1 per 100,000, the female, 2.5. The difference in the rates for the various countries is striking, from a high of 26.1 in Japan to 0.6 in Ireland. The rates for the United States (3.9 for males, 1.6 for females) are considerably below the median.

The mortality from suicide in the 15- to 19-year-old group is highest in Japan (26.1 for males, 18.7 for females in 1952-1954). About 2,000 young persons in this age group took their lives in Japan each year during the period under consideration (1951-1953).

An unusual feature of the Japanese data is the high suicide rate among females. Indeed the suicide rate in Japanese girls, 15 to 19 years old, is higher than the male rate in any other country. Up to the middle twenties the female suicide rate in this age group in Japan exceeded the male. This was not true among adults.

A higher female than male suicide rate among adolescents is also recorded for Ireland and Italy during the years shown in Table IV. The number of deaths from suicide in Ireland is so small that no conclusions can be drawn. In Italy the suicide deaths over the years are approximately equal in the sexes.

Almost as high as the Japanese figures are those from prewar Germany. In 1938 the suicide rate in the 15- to 19-year-old group was 23.5 per 100,000 for boys and 11.0 for girls. During 1932-1934 the rate was even higher—30.8 for males and 16.2 for females.

TABLE IV. MORTALITY PER 100,000 FROM SUICIDE IN SELECTED COUNTRIES, 15 TO 19 YEARS OF AGE, BY SEX

COUNTRY	YEARS	MALES	FEMALES
Japan	1951-1953	26.1	18.7
Switzerland	1952-1954	16.9	6.4
Finland	1952-1954	12.3	2.6
German Federal Republic	1952-1954	12.1	6.8
Austria	1952-1954	11.7	8.1
Union South Africa (European population only)	1951-1953	9.7	2.8
Denmark	1952-1954	8.3	5.9
Chile	1950-1951	7.6	4.3
Portugal	1947-1949	6.9	6.0
Australia	1951-1953	6.2	1.9
Sweden	1951-1953	6.0	3.3
New Zealand (without Maoris)	1952-1954	5.2	0.5
France	1952-1954	4.4	2.4
United States	1951-1953	3.9	1.6
Spain	1951-1953	3.8	2.0
Canada	1952-1954	3.8	0.7
Italy	1951-1953	2.9	3.3
England and Wales	1952-1954	2.9	1.1
Netherlands	1952-1954	2.3	0.8
Norway	1952-1954	2.0	1.0
Scotland	1952-1954	1.9	0.4
Ireland	1952-1954	0.6	1.1

Source: Epidemiological and Vital Statistics Report, Mortality From Suicide, issued by the World Health Organization 9: 243. 1956.

The suicide rates in Germany do not appear to have been influenced by the advent of Hitler. For persons 15 years and over they remained unchanged from 1911 to 1938. The rates in Germany in the 15- to 19-year-old group have fallen markedly since World War II.

High suicide rates in adolescents are also recorded in Switzerland (16.9 per 100,000 for males, 6.4 for females), Finland (12.3 for males, 2.6 for females), and Austria (11.7 for males, 8.1 for females). The lowest rates in this age group are in Ireland, Scotland, and Norway.

The suicide rates in teenagers follow fairly closely the rates in adults. There are, however, notable exceptions. The suicide rate in the 15- to 19-year-old group in Japan is 10.9 per cent of the over-all suicide rate (15 years and over). In Sweden, on the other hand, the percentage is only 0.2. For the twenty-two countries shown in Table IV the correlation coefficient (r) for male suicides is .72.

The suicide rate in the 15- to 19-year age group in the United States has fallen during the last thirty-five years (Table V). In males a rise occurred during 1929-1931 and 1936-1938, but the rates were lower in 1947-1949, 1951-1953 and 1954. The decrease is especially marked in the females. The figures show a steady drop from 1921, when the rate was actually higher in girls than boys, to 1954 when the female rate was only 37 per cent of the male. Reductions have also taken place in Germany, France, Italy, England and Wales, and Scotland. Switzerland shows an upward trend in boys. In Australia the male rates rose and the female rates dropped sharply. New Zealand shows no trend in males but a marked fall in the rates in girls.

In percentage of all suicides in the United States the rates in adolescents 15 to 19 years has dropped, more strikingly in girls than in boys (Table VI).

TABLE VI. DEATHS FROM SUICIDE, 15 TO 19 YEARS, AS PER CENT OF DEATHS FROM SUICIDE AT ALL AGES, UNITED STATES

YEARS	MALES	FEMALES
1921	1.8	6.9
1929-1931	1.9	5.8
1936-1938	2.1	4.4
1947-1949	1.6	2.4
1951-1953	1.6	2.4
1954	1.5	2.1

Suicide is less common in the United States in nonwhites than in whites at all ages (Table V). In the 15- to 19-year-old group the difference is not as marked in girls as in boys.

TABLE V. COMPARISON OF THE MORTALITY FROM SUICIDE IN AGE GROUPS 10 TO 14 YEARS AND 15 TO 19 YEARS BY SEX AND RACE

	WHITES				NONWHITES			
	MALES		FEMALES		MALES		FEMALES	
	10-14	15-19	10-14	15-19	10-14	15-19	10-14	15-19
1921	0.9	4.3	0.5	4.6	0.2	2.8	–	3.2
1929-1931	0.6	5.1	0.2	4.3	0.3	2.4	–	2.7
1936-1938	0.7	5.2	0.2	3.4	0.7	3.2	0.4	2.0
1947-1949	0.8	3.9	0.2	1.9	0.3	2.3	0.2	1.6
1951-1953	0.7	4.2	0.1	1.6	0.5	1.7	0.3	1.4

The most common means of committing suicide by adolescents in the United States (Table VII) is "firearms and explosives." This holds true in both boys and girls. These agents were used by 133 out of 261 teenagers (51 per cent). They were used somewhat more frequently by boys (108 out of 191 cases, 57 per cent) than by girls (25 out of 70 cases, 36 per cent).

The next most frequent means is "hanging and strangulation" in boys, and "poisoning" in girls. In 1954 in the United States 43 out of 191 males (22 per cent) took their lives by hanging and only 3 out of 70 females (4 per cent). On the other hand, 33 out of 70 females (47 per cent) used poison and only 30 out of 191 boys (16 per cent).

10 TO 14 YEARS OF AGE

The mortality rates for suicide in this age group in twenty-two selected countries are shown in Table VIII. For these countries the median rate is 0.65 per 100,000 for boys and 0.2 for girls. The highest rates are recorded in Germany (boys 1.9, girls 0.5). Portugal (boys 1.7, girls 0.3), Denmark (boys, 1.3, girls 0.2), and New Zealand (boys 1.3, girls 0). The lowest rates are those of Norway, Scotland, and Ireland. The rates for the United States (boys 0.7, girls 0.2) are slightly above the median.

In this age group the male rate generally far exceeds the female. In the United States the male rate is three and one-half times the female. The rate in white boys is much higher than in nonwhites; it is about the same in white and nonwhite girls.

The death rate from suicide in children 10 to 14 years old has not varied appreciably in the United States since 1921. It follows in a general way the rate in adults (r = .53). It is more closely related to the suicide rate of the 15- to 19-year-old group (r = .73).

The most frequent means of self-destruction by boys is "hanging and strangulation" (Table VII). This was used in 1954 in the United States by 17 out of 30 boys (57 per cent) and by 2 of the girls. "Firearms and explosives" is next, accounting for about one-third of the deaths in boys and 3 out of 7 girls. Four boys and 2 of the girls used poison.

TABLE VII. THE MEANS OF COMMITTING SUICIDE BY SEX AND AGE, UNITED STATES, 1954

MEANS	NUMBER OF DEATHS					
	10-14 YEARS			15-19 YEARS		
	TOTAL	MALE	FEMALE	TOTAL	MALE	FEMALE
All means	37	30	7	261	191	70
Poisoning	6	4	2	63	30	33
Hanging and strangulation	19	17	2	46	43	3
Firearms and explosives	12	9	3	133	108	25
All other means				19	10	9

Source: Vital Statistics of the United States, 1954, vol. II, Table 50.

TABLE VIII. MORTALITY PER 100,000 FROM SUICIDE IN SELECTED COUNTRIES, 10 TO 14 YEARS, BY SEX

COUNTRY	YEARS	MALES	FEMALES
Germany, Federal Republic	1952-1954	1.9	0.5
Portugal	1947-1949	1.7	0.3
Denmark	1952-1954	1.3	0.2
New Zealand (without Maoris)	1952-1954	1.3	–
Finland	1952-1954	1.2	0.4
Switzerland	1951-1953	1.1	0.4
Japan	1952-1954	0.9	0.5
Chile	1950-1951	0.8	0.5
Sweden	1951-1953	0.7	0.1
United States	1951-1953	0.7	0.2
Austria	1952-1954	0.7	0.3
France	1952-1954	0.6	0.2
Australia	1951-1953	0.5	–
Italy	1951-1953	0.5	0.2
Netherlands	1952-1954	0.5	–
Canada	1952-1954	0.5	0.2
Spain	1951-1953	0.5	0.2
Union South Africa (European population only)	1951-1953	0.2	–
England and Wales	1952-1954	0.2	0.1
Ireland	1952-1954	0.2	–
Scotland	1952-1954	–	0.2
Norway	1952-1954	–	0.3

Source: Epidemiological and Vital Statistics Report, Mortality From Suicide, issued by the World Health Organization 9: 243, 1956.

UNDER 10 YEARS OF AGE

Of special interest to the pediatrician is suicide in children under 10 years. It is rare in this age group, only an occasional case having been recorded in the United States mortality figures.

Suicide in young children must be considered in the light of their incompletely developed concept of the meaning of death. According to Schilder and Wechsler,[18] whose studies were carried out on the children's ward of the psychiatric service of Bellevue Hospital, young children deal with death and its paraphernalia in a matter-of-fact and realistic way. They comprehend that death means immobility and insensitivity and they understand the meaning of coffins, burial, cemeteries, and the like.

By and large, children are not concerned with their own death even though, having observed the death of others, they are willing to concede its possibility. They disbelieve strongly that they will die. When the child considers his own death at all he projects it far into a future which has for him no reality. Death is only for the aged. It is remote; it is so distant an event that it is no cause for concern. Nevertheless children almost universally declare that they do not want to die, even though they may just have declared how nice it is in heaven.

Death from disease is accepted but it is generally associated with the idea of violence and even dismemberment. The idea of death by violence is deeply ingrained in the child's mind. His attitude toward death, whether agreeable or disagreeable, is to a large extent determined by the attitude of the parents.

Very young children often regard death as reversible. Even later on it seldom has the character of something definite and final. It is therefore easy for children to wish the death of others—or themselves—and to speak of killing people without any conscience-stricken feeling.

The results of studies on Hungarian, Swiss, English, and other groups of American children are in general agreement with those of Schilder and Wechsler (summarized by Bender[5]).

Redlich and Lazar[14] in 1914 presented a number of case histories of suicide in young children gleaned principally from newspaper accounts. Their youngest patient, and the youngest recorded case of a suicidal attempt, was a 3-year-old boy. He and his sister aged 1½ years were found unconscious in a gas-filled room with the gas jet open. The children were revived with great difficulty. The boy said that he wanted to kill himself and his sister because his mother would not take him for a walk. Earlier in the day the child's father had told, in the child's presence, about a young man who attempted suicide with illuminating gas.

An attempt by a 3-year-old boy to hang himself is reported by Baer[13] but here the child was playing and had no intention of killing himself.

Several suicides or suicidal attempts have been reported in 5-year-old children.[10, 11, 13] Redlich and Lazar[14] relate the case history of an alert, well-brought-up 5½-year-old boy. He had been scolded by his mother. Shortly afterward he brought his father his lunch. On the way home, he deposited the luncheon pail

on a bridge and jumped into the river Mur. He disappeared at once and his body was found several hours later. He had told his mother repeatedly that he was unhappy and that he would jump into the water. Autopsy showed striking changes in the brain.

Another 5-year-old reported by Redlich and Lazar was a girl who attempted suicide by jumping out of a window. The window was not very high and she sustained only minor injuries. She came from a home in which she was badly treated.

We have observed a 5-year-old boy who made repeated attempts at suicide.[19]

CASE HISTORY.—Henry, 5½ years old, jumped or fell out of a seventh-story window. He got up and tried to walk but collapsed and was stuporous for five days. The small bones of one foot were broken. Recovery was complete. He was admitted to the Children's Psychiatric Division at Bellevue Hospital for study, but he was removed by his parents after forty-eight hours, before any conclusion was reached about him.

Henry was the oldest of three children. During pregnancy the mother had had a "kidney condition" and was "swollen." He was born at term without difficulty. He had measles at 1 year.

Thumbsucking started at 11 months and continued until almost 3 years of age. At 5 months he began to bang his head. This became worse with time and he would strike his head against a hard object like the floor or a stone wall whenever he was frustrated. The habit lasted until he was 2 years old. At this time he was described as very aggressive, negativistic, bossy, quarrelsome, talkative, and overactive. His I.Q. score on the Goodenough "Draw-a-Man" test at 4½ years was 127.

The first suicidal attempt was made at 3½ years, when Henry stepped out of a first-story window. Shortly thereafter he was found hanging by his arms from the fire escape. At about this time he fell down a flight of stairs and bruised his head. He was also injured in a revolving door. At 4 years, following a severe beating, he said he was going to jump out of the window. He repeated this threat whenever he got angry. The parents' reply was to "go ahead."

He made numerous other attempts at self-destruction. At 5 years, 4 months, while being taken to a play group in a bus, he would repeatedly leave the bus when it stopped, and rush out into the open road among the moving cars. When he saw an exceptionally large dog he would put his hand into the dog's mouth. He would ride his bicycle in front of automobiles moving toward him. The kindergarten teacher reported that he tried to smother himself under a blanket. The camp director notified the mother that Henry was "out to kill himself." When cautioned that he would hurt himself he said, "I want to get hurt" and "I want to break a leg."

The mother was dull mentally and rather passive. A sister of the mother characterized her as loving the child with "a love which is so intense it is abnormal." The father was foreign born and was described as dictatorial in his attitude toward the children. He had been previously married and divorced. He spanked the boy repeatedly. When Henry was 2 or 3 years old, his parents tied him in his crib because he tried to get out and leave the house. Henry was very antagonistic toward his father and hated him. He was intensely and overtly jealous of his father's relationship with his mother. At the same time he seemed to feel guilty about his feelings and wanted to punish himself.

Henry indulged in all sorts of mischievous tricks, such as pulling off

the tablecloth and strewing china and silver on the floor, throwing his father's lamb chop into the garbage pail, and emptying the saltcellar into his mother's coffee. When spanked he would not cry, but would say "give me more."

At 8½ years, Henry had not voiced any more suicidal threats nor made any more suicidal attempts since he jumped out of the window. His behavior was still troublesome. He was described as "high strung, uncooperative, very disobedient." He had no interest in school, and his schoolwork was very poor. His resentment toward his father continued.

He had completely recovered from his fall. When asked what his three magic wishes would be, he answered (1) to be a famous man, (2) to have lots of money, and (3) to live forever. His dreams were, for the most part, bad ones. An oft-repeated dream was about Jack and the Beanstalk. He was the giant and fell off the beanstalk. He woke up just in time to save himself. He also had "love" dreams. He dreamt about a man named Tex. "Tex proposed to a girl. Everytime she said no and slapped him in the face. Then Tex killed the girl. He killed 16,000 girls."

At 13½ years, he was still a "terriffic problem." His schoolwork was very poor. He created disturbances in the classroom and seemed to enjoy flaunting authority. He was resentful against his father who now treated him gently and kindly. The father was outwardly calm and easygoing. Henry fought with his mother continuously.

Suicide in a 7-year-old boy was described by Redlich and Lazar.[14] The youngster's parents left him at home to watch his grandmother. He was heard to call her and to cry out several times that he would throw himself out of the window if he could not find her. Soon afterward he actually jumped out of the window and was killed. The boy was born after a difficult delivery; he had convulsions and was regarded as feeble-minded at school.

An 8½-year-old boy, also described by Redlich and Lazar, had taken money from his mother. She discovered the theft shortly and caught the boy on the street after he had spent some of it. When his father came home in the evening the boy ran to the window of the third-story apartment and jumped out. He sustained only minor injuries. He was a badly behaved, disobedient, mischievous youngster given to stealing and setting minor fires.

Baer[13] gives brief case histories of three boys under 10 years who made serious suicide attempts, two of them fatal. A badly behaved 8-year-old child, who had been truant from school repeatedly, was locked in a closet by his father. He escaped and jumped from a fourth-story window onto the asphalt pavement below, sustaining only a fracture of the leg. A 9-year-old boy threw himself into the river Spree and drowned. He had read robber stories and talked much about murder and suicide. He ran away several times and was brought back by the police. He disappeared from home one day and was found in the water. Another 9-year-old boy described by Baer had been scolded by his mother and punished by his father because of truancy. That same evening the boy jumped out of a fourth-story window and died later of multiple injuries.

FACTORS LEADING TO SUICIDE

General Considerations.—Certain generalizations regarding suicide hold during the childhood years as well as

later on. Suicide is more common in males than in females and in whites than in nonwhites. Urban dwellers outnumber rural, and professional groups (and students) outnumber workers.

The over-all suicide rate fluctuates according to the season of the year. For example, in the registration area of the United States, 1910-1923, the rate was highest in May.[20] It fell during the summer and autumn, reaching its lowest point in December. Throughout the winter months the rates rose gradually to the high point in May. Taking the mean for the year as 100, the seasonal variation was considerable, the difference between the high and low rates being as much as 35 points. Similar seasonal variations have been observed in other parts of the world.

The seasonal fluctuations are not related to temperature, mean relative humidity, precipitation, or wind velocity. It is of some interest that the seasonal swings are wider for females than males (Massachusetts, 1910-1923[20]).

Mulcock[8] found a similar seasonal variation in the incidence of suicide in children 8 to 17 years of age, the deaths being most frequent from March to July. It might be supposed that the high rates during these months are related to the strain of school examinations; but this would hardly account for the similar seasonal variation in adults.

Religious affiliation exerts a strong influence on the incidence of suicide.[20] Aside from the fact that religious doctrine offers solutions to many of the problems which harass man, membership in a church means belonging to a group with which the individual can identify and from which he can derive the means of satisfying his social needs. The firmer the church organization and the more devoted the members to their beliefs, the more fully are personal problems resolved.

It is therefore to be expected that suicide will be relatively uncommon among Catholics and this is actually the case. In general, suicide rates are lower in Catholic than in Protestant countries, and in various countries with large mixed populations a similar difference obtains. Potent factors here, also, are the bitter opposition of the Church to self-destruction and the strong hold which it exerts on its members.

Suicide rates were low among European Jews during the nineteenth century but they rose sharply during the early decades of the present century.

There have been many epidemics of suicide.[20] Most of these took place in ancient times. In some instances large numbers of soldiers took their lives to avoid capture by an enemy; at other times the motive was to achieve martyrdom, or religious fervor.

In England in 665, the mortality from pestilence was so high that many persons crowded the seaside and threw themselves from the cliffs, preferring a speedy death to the lingering torments of illness. In Russia in 1666 whole communities killed themselves during a revival of religious fanaticism. In 1897 twenty-eight persons buried themselves alive in Tiraspol to escape the census enumeration which they apparently regarded as sinful. At various times epidemics of suicide occurred among

Jews to avoid persecution and torture. In York, in 1190, over 500 died by their own hands.

As recent as 1928 an epidemic of suicide in Budapest resulted in 150 deliberate drownings* during the months of April and May. The epidemic was terminated by setting up a squadron of boats or "suicide flotilla" which patroled the Danube and managed to save nine out of ten would-be suicides.

Popow[21] described an epidemic of suicides among school children in Moscow. Within one school district seventy children took their lives between May, 1908, and October, 1910. (Unfortunately the age range is not given in the German abstract of Popow's paper.) The motives were school difficulties—conflict with the school administrator, poor grades, bad examination results; adverse home situations; love affairs; and physical illness. Popow considered imitation an important factor.

Suicide is regarded by many as a trait largely determined by heredity. This idea is not borne out by the studies on twins by Kallmann and associates.[22] They found that one-egg twin partners are not concordant for suicide. In their series of 10 pairs of one-egg twins and 17 pairs of two-egg twins where one twin committed suicide, all of the cotwins remained alive beyond the crucial age period in which the suicides of their twin partners occurred.

The authors consider various possible explanations for their findings. For one thing the surviving twin may be psychologically immunized against suicide. Possibly the deterrents to a cotwin suicide are painful memories of the circumstances and events incidental to the suicide, or the survivor's tendency to identify himself with his suicidal twin so completely that a second suicide would be like taking one's life a second time.

Another possible explanation proposed by the authors is that suicide of a twin leads to dramatic relief of a chronic state of tension produced by a rivalry much more intense than among siblings. By the suicide of a twin, the cotwin is deprived not only of a suitable object for further competition but also of a sufficiently strong motive for his own suicide at a later date.

The authors reject both these mechanisms to explain the discordance among twins and conclude that their data refute the possibility of a special genetic factor predisposing a person to the commitment of self-destruction.

As a rule, they hold, successful suicides "cannot be simply explained by a certain type of personality and genetic constitution, or by a particular combination of social frustration and personal distress, or by the effect of a special psychotic syndrome." Though each of these may play a part, they cannot be expected in themselves to lead to suicide even if all these factors are present together. The successful suicidal act seems to be "a compulsive and certainly abnormal type of short-circuit reaction of a person in distress." It has been described as a "twilight state of self-destructive ecstasy" in response to the inability to adjust to adverse life pressures. The circumstances under which the self-destructive action takes place must be the outcome of

*New York Times, July 27, 1928.

such a peculiar combination of motivational factors as to render a duplication of this high-tension state unlikely, even in one-egg twins.

Another current idea, that suicide is more common in only children than in children who have brothers and sisters, was also investigated by Kallmann and associates. Their results indicate that the percentage of only children who die of suicide is no greater than the percentage of only children who die from other causes. They conclude that the number of only children with self-destructive tendencies does not differ significantly from the expected number as deducted from data available with respect to the general population.

SOCIAL FACTORS

The "social" causes of suicide have been emphasized by Durkheim.[23] He pointed out that the suicide rate of any particular nation remains fairly constant over a period of years and differs consistently from that of other nations. It follows from this observation that there are causes for suicide which are outside the individual and which have to do with the social milieu. The importance of the social factors can be inferred from the magnitude of the variations in the suicide rate in different countries. The male suicide rates in adolescents 15 to 19 years of age vary from 0.6 per 100,000 in Ireland to 26.1 in Japan (Table IV); the rates in boys 10 to 14 years from 0 in Norway and Scotland to 1.9 in Germany (Table VIII). Durkheim groups the social factors in three categories:

1. Durkheim proposed that the suicide rate of a community varies with the extent to which each individual feels that he is a part of the controlling social group. If the group loses cohesion it can no longer exercise its function and the individual's striving will lack purpose and meaning. As a result the suicide rate rises in times of social and economic disturbance. So, also, the rate is relatively high in classes and occupations which are least subject to the common mores.

Durkheim's studies have been elaborated and extended by a number of American workers[24] and, most recently, by Sainsbury.[25] He observed consistent differences in the suicide rates of London boroughs over a period of three decades in spite of considerable changes in the composition of their populations. The suicide rates were significantly correlated with such characteristics as social isolation (e.g., people living alone or in boardinghouses), social mobility (e.g., daily turnover of population and number of immigrants), divorce and illegitimacy. The rates were higher in middle-class groups than among the poor. Unemployment and overcrowding were not significant factors. The rate was increased by social conditions which led to a sudden fall in the standard of living.

2. To explain the frequency of suicide in societies where there is seemingly great integration of the individual into the group and where the individual is rigidly governed by custom and habit, e.g., Japan, Durkheim proposed that here the basis for the act is altruistic, the inividual taking his life because of noble ideals, religious sacrifice, or blind allegiance.

3. A third basis for suicide proposed by Durkheim is characteristic of

times of economic crises. The self-destructive act results from a failure of the individual to adjust when social restraints are weakened during periods of stress.

The variability in the death rate from suicide is wider in children and adolescents than in adults. This is shown in Table IX where the coefficients of variation for the death rates in twenty-two countries are compared. The coefficients are considerably higher for the age groups 10 to 14 and 15 to 19 than for adults 15 years and over. This means that external factors are even more important in children and adolescents than in adults.

TABLE IX. THE VARIABILITY OF DEATH RATES FROM SUICIDE IN TWENTY-TWO COUNTRIES BY AGE

AGE (YR.)	COEFFICIENT OF VARIATIONS*
15 and over	50
15-19	63
10-14	63

*The coefficient of variation is the standard deviation multiplied by 100, divided by the mean.

The suicide rates in children and adolescents correlate fairly closely with the rate in adults. It follows that, to a considerable extent, similar external factors affect the incidence of suicide at various age levels.

Durkheim's analysis of the social factors leading to suicide fails to explain the marked differences in the rates in Western countries. It is hard to believe that the much higher figures for Denmark than for nearby Norway are due to greater social isolation in Denmark.

It seems likely that the strictness of a social system, as exemplified by the "Prussian" way of life, is a major factor leading to suicide. The rigid conformity expected of its members allows too few alternatives. From the very beginning the child is reared in an atmosphere which demands strict conformity and which brooks few transgressions. Punishment is prompt, frequent, and severe. This attitude is dominant not only in the home, but also in the school and, later on, in the community.

Another social factor of major importance is the popular attitude toward the suicide act. In the United States, England, and elsewhere suicide is looked down upon as a cowardly act or as the act of a sick person. In other countries, notably Germany and Austria, it is generally regarded as an honorable and noble way to die. Germany has been referred to as the land of "romantic suicide." Within a short space of time in recent years, three of Vienna's most distinguished pediatricians—Pirquet, Knoepfelmacher, and Leiner—took their lives.

In this presentation a discussion of suicide in Asian countries has been omitted since the conditions are unique and do not apply here or in Europe. For example, it was once the rule in India for the wife to kill herself when her husband died, a custom known as "suttee." At times it has also been expected that the servants will commit suicide when their master died. It is of interest that formerly, in Japan, the children of the nobility and military classes were familiarized with the idea of self-destruction from their earliest years. They were taught that existence must be surrendered when duty or honor demands.

INDIVIDUAL FACTORS

The number of reported suicides and serious suicidal attempts in children under 10 years is so small that generalizations regarding motivation can only be made tentatively. For the most part the children are badly treated at home and react with rebellious behavior. The suicidal act is usually precipitated by fear of punishment.

The 5-year-old boy described above who jumped out of a seventh-story window does not fit into this category. He was well treated at home and had the affection of his parents. He was inordinately jealous of his father's attentions to his mother and strong feelings of guilt seemed to be his principal motive for self-destruction.

Hall[26] regards the widespread desire to punish others who will be grieved by their death as one of the most frequent motives to suicide in young children. An angry child, unable to punish directly those who have injured or insulted him, seeks in self-destruction to take his revenge on those who love him. This motivation is more common in the girl and is likely to persist longer.

Among the reasons for suicides below the age of 15 years in Prussia, according to Baer,[13] remorse, shame, and pangs of conscience rank high, being major considerations in about one-third of the cases. Mental illness accounted for less than 10 per cent of cases. Other reasons were anger and quarreling, passion, being fed up with life, physical suffering, worry, and depravity. In about one-third of the cases no cause could be found.

It seems reasonable to assume that the high suicide rate among Prussian children was related to the overly strict "Prussian" attitude toward children and the children's fear of punishment in the home and, perhaps even to a greater extent, in the schools.

Bender and Schilder[4] in 1937 reported six children below the age of 10 years who fantasied, threatened, or attempted suicide, none successfully. These children, aged 6, 7, 7, 7, 8, and 9 years old, respectively, came from unstable homes. They had all threatened suicide on repeated occasions and had made serious suicidal attempts. Several were followed into adolescence by Bender. None died by their own hands.

Bender and Schilder regard the suicidal attempt in young children as a reaction to a situation which the child finds unbearable. Most commonly the child is unloved, or he considers himself unloved, the need for affection in such cases being especially great because of a physical defect or illness or because of social deprivation. The adverse home situation provokes feelings of aggression which are directed primarily against those who denied affection. Guilt feelings, engendered by the aggressive tendencies toward the parents or parent substitutes, lead to the aggressive feelings being turned against the child himself. Factors which tend to increase aggressive feelings, such as the example of an aggressive parent, favor the drive for self-destruction. The suicidal attempt, further, represents a way of punishing the environment and a method of getting a greater amount of love.

The motives for suicide in children 10 to 15 years have been listed by Baer[13] (Table X). His analysis is based on 936 cases in Prussia for the years 1884-1898. Of first importance are remorse, shame, and pangs of conscience, these being major considerations in about one-third of the cases. Anger and quarreling were of primary importance in about 10 per cent of the suicides. It is of interest that only 7.5 per cent were attributed to mental illness.

TABLE X. MOTIVES FOR SUICIDE IN 936 CHILDREN UNDER 15 YEARS, PRUSSIA, 1884-1898[13]

	BOYS	GIRLS
Remorse, shame, pangs of conscience	32.7	37.3
Anger and quarreling	9.8	11.4
Mental illness	7.5	10.4
Passion	2.6	1.5
Fed up with life	1.8	1.5
Physical suffering	1.9	2.0
Worry	1.5	1.0
Depravity	0.8	1.5
Unknown causes	37.4	31.8

Baer's analysis corresponds closely with that of Morselli[9] made in Prussia for the years 1869-1872. Precipitating factors were an unhappy home, fear of punishment, difficulty at school, and injured pride.

Schachter and Cotte[7] studied 36 subjects, 25 girls and 11 boys, aged 7 to 19 years, who attempted, simulated, or were obsessed with suicide. The children often came from homes broken by divorce, separation, abandonment, or death of a parent. The motives were rebellion against the parents, lack of parental affection, protest against restriction of liberty, fear of imprisonment after antisocial acts, unhappiness in love, jealousy, wounded pride, reproofs.

A study of suicide in young persons in Massachusetts was reported by Stearns[6] in the ten-year period 1941-1950 in which 81 youngsters (60 males, 21 females) under 20 years took their lives. Of these, 18 were between 11 and 14 years and 63 were in the 15- to 19-year group. One-third took their lives by hanging, another 33 per cent by firearms, 15.5 per cent used gas, and 11.3 per cent poison.

Stearns[6] calls attention to a unique group of teen-age boys who committed suicide by hanging. Nearly all of them were between the ages of 11 and 16 years (22 out of 24 cases). The age distribution was as follows:

Age (Yr.)	*No. of Cases*
11	3
12	2
13	1
14	8
15	3
16	5
17	1
18	0
19	1

They were, for the most part, fine youngsters with a record of good health, good personality, good standing in the community, showing leadership qualities, who for no obvious reasons hung themselves.

The act took place abruptly in the midst of what seemed a well-adjusted life. Usually there was some change of clothing, in some instances all clothes were removed, in others they used bits of female clothing like a brassière or girl's stockings. Frequently the boys tied up their hands and feet. They might be chained, padlocked, bound with strings or adhesive tape. Sometimes pin-up types of alluring female nudes were set out within view.

Similar cases are seen not infrequently by medical examiners in

large centers. It is Simpson's[27] view that these hangings are accidental rather than suicidal and that they are for the purpose of masochistic enjoyment of simple restraint or pain. Evidence in favor of Simpson's thesis is found in a recent case report by Shankel and Carr.[28] They studied a 17-year-old boy who, since early adolescence, had frequently dressed in female clothing and masturbated. On several occasions he had hanged himself. He did this, he said, because it produced erections after which he masturbated.

In New York City it is the custom, whenever doubt exists, to record these cases as accidental. A typical case related by Dr. Milton Helpern, Chief Medical Examiner, was that of a 14-year-old boy, seemingly normal in every respect, who frequently indulged in pranks. The parents, on returning home one evening, found the boy, dressed in some of his sister's clothes, suspended from the doorway leading to the living room. Presumably he had chosen this prominent place so that he could be seen by his parents as they entered the house from outdoors and turned on the lights. Since doubt existed as to this boy's intentions in hanging himself the death was recorded as circumstances undetermined.

The predilection of boys for hanging is emphasized by Mulcock[8] who lists 112 deaths by hanging or strangulation in boys and only two in girls aged 10 to 15 years during the years 1935-1949 in England and Wales.

Mulcock[8] points out the multiple factors which lead to a situation where the child sees no way of handling a problem except suicide. The circumstances are no different from what others are up against, but the children who actually commit suicide or make a serious attempt at it seem ill-equipped to cope with such problems owing to inadequate homes, parental indifference or rejection, and lack of cooperation between school and home.

Among the personal factors which predispose to suicide Mulcock mentions physical defects producing feelings of inferiority, hormonal changes accompanying adolescence, anxiety associated with pubertal changes, realization of some sexual abnormality, sex contacts and experiences, difficulty in social adjustment, a hereditary or familial weakness, personality disorders, psychosis, and low intelligence. Predisposing features in the environment are a home broken by divorce, separation, death, and so on, unaffectionate parents, neglect, mental instability of members in the home, friction with siblings, feelings of exclusion, a feeling of being unwanted, school difficulty, and friction with teacher or schoolmates.

At the University of Michigan suicide accounted for over half the deaths among students in 1932-1933.[29] In a five-year study at the same institution suicide or the possibility of suicide was an important consideration in 0.54 per cent of the students (313 out of 58,070).

The incidence of suicidal attempts was highest among freshmen and nonprofessional undergraduates. On the basis of a brief inspection given at the time of entrance examination 47 per cent of this group were regarded, from the standpoint of personality make-up and integration, to

be candidates for problems of adaptation to university life. This is considerably higher than the figure of 27 per cent for students in general.

Of the 313 students, a diagnosis of psychosis was made in 44. The largest group was made up of psychoneurosis or psychoneurotic reactions (153 cases). In 95 cases there was simple reactionary depression and in 21, psychopathic personality.

The most frequent precipitating factor in the suicide attempt seemed to be anxiety over schoolwork (96 cases). Other common precipitating factors were "aspect of a psychotic situation" (44 cases), concern over a love affair (33 cases), anxiety over the sex problem (22 cases), and difficulty in social adaptation (18 cases). In no instance was a single factor involved. Actually the median for the total factors was 22.18 per person.

Raphael and co-authors[29] describe the suicide-prone individual as oversensitive, shy, self-conscious, and inclined to overact, to worry, and to be emotionally delicately balanced. He seems immature and infantile in his understanding, attitudes, and judgments; timid, fearful, and unsure of himself in the presence of everyday life experiences; and concerned about his ability to cope with the academic situation and its responsibilities. He responds readily with fatigue and even exhaustion.

Further he is a poor mixer. He has inadequate recreational outlets, marked feelings of inferiority, and a tendency to self-pity. He shows little initiative and his living habits are poorly organized. He tends to react emotionally rather than intellectually. He worries about the future and is indecisive about choice of a career. Effective sex adaptation is likely to be poor.

In the study by Raphael and associates, though made during the depression years, financial considerations were relatively unimportant. The authors regard the suicidal situation as largely determined and motivated subjectively. The outstanding element seems to be a vulnerable personality which is unable to meet everyday life experiences and everyday problems in an integrated, understanding, and effective manner. They regard the extrinsic component as playing a minor part.

SUICIDAL ATTEMPTS

Suicidal attempts, preoccupations, and threats are frequent in children. An almost universal fantasy, especially among the younger ones, is "If I die then my parents will feel sorry." Childish suicidal attempts are, in the overwhelming majority of cases, not serious. Many are, for the most part, merely self-mutilating acts, without real suicidal end in mind, carried out as self-punishment for actual or imagined misdeeds.

Whereas suicide is more common in boys, attempts are more frequent in girls. They are, presumably, more likely to take out their aggressive impulses against themselves rather than others. By and large these children grow up into normal adults.[5, 29]

A study of suicidal attempts from the Veterans Administration Hospital in Los Angeles County, California, was reported by Shneidman and Farberow.[30] They conclude that suicidal behavior, whether threatened or attempted, should be taken seriously.

Three-fourths of the subjects (veterans) who actually committed suicide had previously made threats or attempts. The authors urge that special caution be taken for ninety days after an emotional crisis has been passed. Almost half the persons who took their lives did so within this period, even though they seemed to be recovering from their troubles.

A hint as to the real intentions of the suicide-minded person may be gained from the type of suicide note. A person who makes a serious attempt to take his own life is likely to include in his note orders and admonitions, as if he had reached a final decision to leave this world and had resigned himself to his departure.

An interesting finding in Shneidman and Farberow's study was that persons who threatened suicide were more disturbed, on the whole, than those who attempted it. It seemed almost as though the attempt had acted in a therapeutic way and had lightened the gravity of the personality disturbance. Such a therapeutic effect, however, was not always permanent and the self-destructive tendency might return.

DISCUSSION

As the over-all death rate in adolescents has fallen, owing principally to control of the infectious diseases, suicide has emerged as one of the leading causes of death in teen-agers. Death is always distressing to relatives and friends who remain behind, but it is especially so in the case of suicide, for here grief is accompanied by shame and by feelings of guilt and inadequacy. Most parents feel that they are in some way responsible for the unhappiness which expressed itself in this extreme fashion.

Fortunately the trend in the suicide rate of teen-agers in the United States is downward, especially among girls. The rate here, as in England and Wales, is well below the median.

The wide fluctuation in the suicide rate from country to country means that factors outside the individual exert a potent influence on the frequency of suicide. What these factors are can only be conjectured.

It is likely that the rigidity of the "Prussian" type of society which is not limited to Germany is an important consideration. In such a society, where strict rules govern minute details of behavior, transgressions will necessarily be frequent. Compliance is based on fear of censure and punishment. There are too few excuses or extenuating circumstances for one who errs; there is too little consideration for human imperfection. Failure to live up to parental expectations at home or at school is regarded as willful misbehavior. Under these circumstances a reaction with strong guilt feelings is natural and this, in turn, expresses itself in a desire for self-punishment.

Important, too, is the social attitude toward the self-destructive act. Where suicide is regarded, to some extent at least, as an honorable and noble way to die as, for example in Germany and Austria, the act will be more frequent than in countries like England and the United States, where suicide is look down upon as cowardly behavior or as a sign of mental aberration. Social acceptibility is a prominent factor in the suicide rate in certain parts of Asia.

Without any explanation are the seasonal fluctuations in the suicide rate. It is true that the high rates during the spring months coincide with "examination time" in teen-agers, but this fails to explain the similar peak in adult rates.

The individual factors within a society which lead to suicide vary according to age. In young children, fear of punishment, remorse, shame, guilt feelings, and anger are prominent factors. Most of the reported cases have come from unsatisfactory homes.

In the teen-ager similar factors operate and, in addition, feelings of inadequacy, feelings of exclusion, and problems of sex adjustment. School problems are taken more seriously by the teen-ager than by younger children. Interesting are the cases described by Stearns and others of hanging in seemingly well-adjusted boys. It is worth noting that mental illness is regarded as a minor cause of suicide, accounting for only about 10 per cent of the cases.

The sole approach to the suicide problem lies in recognizing beforehand the susceptible individuals and in their proper management. Too often suicidal threats and even minor attempts are looked upon as bids for attention and sympathy, which they usually are, and the unhappy adolescent is subjected to teasing and ridicule. Unfortunately tragedy follows in a certain number of cases.

There are a few warning signs that should make the physician suspect impending suicide.[31] Most prominent is depression, often associated with insomnia, instability, and violent temper outbursts. In some instances suicide follows a recent surgical operation or a painful long drawn-out illness. And, last, the type of suicide note may give helpful information.

Sifneos and associates[32] emphasize the value of hospital care as a preventive measure. The hospital helps by removing the person from the acute situation which is troubling him. It provides a dramatic demonstration that his concerns, practical and psychological, are being seriously considered and that something is being done for him. Physical ailments are attended to. And, finally, psychiatric treatment is provided.

An interesting approach to the suicide problem suggested by Watney[33] is the creation of a society on similar lines to Alcoholics Anonymous. This would be a permanent service which would be prepared to accept calls from any person seeking help. It might be possible to prevent suicide in some instances if a sympathetic listener could be found who would give assistance and encouragement. The persons chosen for this work would, preferably, be ones who had themselves overcome a similar problem in the past.

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Pediatric Profiles

Sir Thomas Barlow

(1845-1945)

BARLOW is remembered today mainly for his work on infantile scurvy; indeed in some European countries the condition is known as Barlow's disease. This and his other contributions to medical knowledge were completed well before the end of the nineteenth century and undoubtedly brought him into the front line of medical research workers at that time. But although he published little of importance after the last few years of the century, his reputation as a physician continued to increase until, during the first fifteen years of the present century, he was considered one of the leading members of the profession. Specialization is rather a recent phenomenon in medicine, and although Barlow devoted much of his time to the care of children, he never confined himself to this age group. Indeed, when he was first appointed to the consultant staff at University College Hospital, even surgery was not entirely independent, for all patients were admitted under the care of the physicians, and only at their request could a surgeon be called in. He was not the first to describe scurvy in infants, but his work, by its scope and thoroughness, convinced the medical profession of the existence of such a condition; moreover, he was able to demonstrate the invariable use of artificial feeding prior to its development and the curative effect of fresh food. His suggestion that fresh food should be included in the diets of all artificially fed infants from the age of 6 months had a great influence on the future of infant feeding and was a step in preventive medicine that was to have far-reaching results.

Barlow's work on scurvy explains and justifies to a large extent the

high esteem in which he was held internationally, while in England the continued advance of his standing in the medical profession was also due in great measure to his clinical ability and value as a consultant.

He was born in Edgeworth near Bolton, Lancashire, in 1845. He was the son of a cotton manufacturer, who naturally wished his elder son, Thomas, to carry on the business. But Barlow had no inclination for such work. At an early age he had developed an interest in science, particularly natural history and geology, and he wanted a scientific or medical career. A diphtheria epidemic during which two of his family died when he was 16 years old, although no uncommon event in those days, may well have influenced him in his final choice of medicine. His father persuaded him to enter the family business for a trial period, but it very soon became apparent that he was not suited for that kind of work, and he was allowed to follow his own desire and went to Owen's College, Manchester, to read chemistry. A year later, in 1866, he went to University College, London, to study medicine. Having a few months to spare before starting his medical course, he spent them in a tour of Palestine. The choice of Palestine may have been determined by his religious upbringing, but while there, he by no means confined himself to scriptural matters, since he spent a good deal of time collecting plants, pressing and mounting them in albums while riding on a mule between one village and the next.

He prolonged his preclinical studies rather more than was usual, doubting whether he would be successful in clinical work, but when he did change over, to use his own words, he "got on like a house on fire" and felt that he had really found his métier. He qualified in 1871, and in 1875 he was planning to go to Vienna for a few years when he applied for and was appointed to the post of registrar at The Hospital for Sick Children, Great Ormond Street, London. The following year he was made assistant physician, ten years later he became physician, and he retired from the staff in 1899. For short periods he was on the consultant staffs of the Charing Cross Hospital, the London Hospital, and The London Fever Hospital. In 1880 he was invited to become Assistant Physician at University College Hospital and remained there until 1910.

It is not easy now to find firsthand accounts of his early life, but one of his fellow students was Sir Rickman Godlee whose career as a successful surgeon at University College Hospital ran parallel to that of Barlow as a physician, and who was president of the Royal College of Surgeons at the same time that Barlow was president of the Royal College of Physicians. Godlee describes him as of short and stocky build, robust, and full of energy. Barlow was a tireless worker, often to be found in the wards till well after midnight. He could evidently manage with very little sleep, for another colleague of his, who was addicted to early rising, frequently found him still reading at 6 o'clock in the morning. His desire always to use his time profitably is well illustrated by an event which occurred many years later. At the age of 85, in a town in the southern part of France, he was left alone in the

car for rather a long time; when his daughter returned she found a crowd surrounding the car and Barlow holding the side of the car doing knee bends and other exercises.

Godlee also tells us that Barlow was conspicuous among his contemporaries for the unconventionality of his dress. He is described as a "spectacled and bearded figure in a suit of dittos" (a suit of clothes of the same material throughout). These probably suited his short, stocky figure and blunt, straightforward manner, but after his marriage, his wife took such matters in hand, and so long as he did not himself have the bother of considering or ordering his clothes, he readily agreed to wearing the conventional top hat and frock coat of the doctor of his day.

His politics were also considered unconventional, for he held advanced liberal views which earned him the nickname "Citizen Barlow." With the Russian revolution closer in our memories than the French revolution, perhaps he would nowadays have been known as "Comrade Barlow." He was also sometimes called Sir Thomas de Barlow which suggests that his contemporaries found the revolutionary elements in his character mixed to some extent with more aristocratic ones. The former side found expression in his deep sympathy with the hospital class of patient, which persisted throughout his life. A. E. Barton, who worked as his clinical assistant, says, "His kindly treatment of outpatients began to have a definite influence among us, till at last it was looked on as 'bad form' to bark at the sick." Which, incidentally, throws some light on the general attitude to hospital patients at that time. His second nickname may have been due to a certain aloofness. While he was a student and for several years after qualification, he led a very solitary life, absorbing himself completely in his work. He went to many concerts and enjoyed an occasional play, but the main social event each week, until after his marriage in 1880, was Sunday lunch with his landlady.

The year 1880 was always referred to by Barlow as his "annus mirabilis," partly because of his attaining the fellowship at the Royal College of Physicians and of the invitation to University College Hospital as Assistant Physician, but chiefly because in that year he met, and on New Year's Eve married, Ada Dalmahoy of Edinburgh. She had been the sister of his ward at Great Ormond Street, and was one of a group of young Scotswomen who came to Great Ormond Street, perhaps under the influence of the matron, Miss Dalrymple Hay, to train as what were then called "lady probationers." After a few months' training they were able to be promoted, if it were considered suitable, to be in charge of one of the wards or other departments. His marriage undoubtedly transformed Barlow's private life and widened his social contacts. His wife's gaiety and humor lightened his somewhat overserious outlook, and the zest with which she shared his interests, as well as her confidence in his abilities, served to dispel the moods of depression and self-depreciation to which he had always been subject.

They had three sons and two daughters, of whom the younger daughter died in infancy and the third son died in the First World

War. His other daughter, Helen, Barlow, remained at home and gave much of her time to helping him, both in his work and in his social activities. After his wife's death in 1926, he came to rely on Helen to an ever-increasing extent, and her cheerfulness and energy made her a delightful companion for their travels abroad and greatly enlivened his declining years.

After he had qualified, he became house physician to Sir William Jenner at University College Hospital. This was a most significant factor in his development, for he learned from Jenner the value of extreme accuracy in clinical examination with attention to even the most minute details, and also the fundamental importance of exact post-mortem studies and their correlation with clinical findings. Barlow applied methods which Jenner had himself used when he differentiated typhoid fever from typhus, and these methods enabled Barlow to make his work on scurvy more convincing.

Barlow certainly performed his post-mortem examinations carefully. One of his assistants recollects his turning away at the end of a post mortem when there was nothing left on the table of a size larger than a lump of sugar, saying, "Ah, well, I don't think it would be right for us to go any further." Post-mortem examinations were often carried out under considerable difficulties in those days. When the child died at home, the post mortem usually had to be done there too, sometimes with the general practitioner as assistant and the child's relatives as an audience. In any fatal case where Barlow had had a difference of opinion with the general practitioner or another consultant over the diagnosis, he made every effort to hold a post mortem and to get those whose opinions differed from his own to come and see it. In this way he was often able to verify his clinical impressions, for he undoubtedly had a flair for accurate diagnosis, and he would then take much pleasure in correlating the pathological with the clinical findings and showing how he had reached the correct diagnosis on clinical grounds. Even when post mortems were carried out at Great Ormond Street, conditions were far from ideal; he once said that it was an advantage to get down to the post-mortem room early, before the day's supply of candles had run out.

At a time when there were few ancillary aids to diagnosis and a physician had to rely almost entirely upon evidence derived from his own senses, meticulous care in examination and a good memory for detail were of great value and account for much of his success. The story is told that when one of his colleagues at Great Ormond Street had inadvertently seen one of Barlow's patients, the mother said that she preferred the other doctor, because he merely had looked at the child and then prescribed treatment, whereas Dr. Barlow had spent over half an hour on the examination and even then did not seem quite certain what was the matter.

He was always cheerful, good humored, and encouraging when dealing with people who came to seek his advice and was never known to lose his temper with a patient or even to speak an unkind word. However, he could be pretty sharp with his house

physician or nurses if he thought that their care was in any respect lacking. He was well aware that many of the symptoms that brought patients to his clinics were the result of poverty and malnutrition and often, instead of prescribing drugs, would dip his hand into his pocket and give the patient a small sum saying, "Poor soul, what she needs most is kitchen medicine." His reputation for this weakness sometimes led to his old patients waiting for him and accosting him in the street, but even then he seldom had the heart to refuse. He took great personal interest in his patients and often developed lasting friendships with them. The lady who said, "Dr. Barlow, I think your conversation does my husband more good than your medicine," may have been perfectly right.

Robert Bridges, who gave up his medical career for literature and later became Poet Laureate, describes Barlow's relationship to patients very well in his *Recollections:* "Among my colleagues there was one man in whom I saw, in their full perfection, the gifts which I lackt, Thomas Barlow with whom I workt at the Children's hospital and who has ever since been a dear and good friend. . . . Of all the doctors I ever knew he was the one who had most intimate personal sympathy with his patients. It is of course not only somewhat dangerous for a physician to allow such feelings full play—they may disturb his scientific judgement—but to bestow a genuine fellow feeling on all your patients daily is a burden which it needs almost superhuman effort to assume, to say nothing of the difficulty of sustaining it. But Barlow's fellow feeling was inexhaustible and unwearied. So far was it from injuring his judgement that it led him often to a sounder and clearer insight into his cases; and while it strengthened his own hopefulness and determination, it also helped his patients towards recovery by evoking the emotional side of their confidence."

His interest in the human side of his patients was reflected in their devotion to him. One of them was a shopkeeper's wife whom he had successfully treated for pneumonia—as he expressed it, "they were good enough to think I had saved her life." Her husband sent him a present of handkerchiefs every Christmas for the next thirty years.

I once treated an old lady at University College Hospital; when she discovered that I was related to Sir Thomas Barlow, and that he was still alive (this was in 1944), she was quite overcome with emotion, telling me that she had been a patient under his care over fifty years previously. He had been at that time the leader of the King's Cross Bible Class which she attended, and they still remembered him there and often spoke about him. His work among the poor in the district around University College Hospital and Great Ormond Street enabled him to gain a far greater insight into their problems than could be achieved from the wards and outpatient department alone and helped, no doubt, in the management and treatment of his patients.

He rarely gave lectures; most of his teaching was done at the bedside and in the outpatient clinic. On his ward rounds he would sometimes sit for what seemed an interminable

time, completely absorbed in the patient at his side. This caused some impatience among his students, but often a penetrating observation at the end of one of these reveries would show the value of unhurried reflection.

When any distress or embarrassment to the patient might result from too frank a discourse upon his case, he would wait until leaving the ward before starting such a discussion.

In the early part of his career he made a number of contributions to medical knowledge, especially in the field of pediatries. In 1878 he wrote a paper with Samuel Gee published in the *St. Bartholomew's Hospital Journal*, showing that the purulent forms of meningitis (which they called simple meningitis) could be differentiated on clinical grounds from tuberculous meningitis, and, later, in an article in *Allbutt's System of Medicine*, written with D. B. Lees on nontuberculous meningitis, the posterior basic form was described as a group of cases which could be separated on clinical as well as morbid anatomical grounds from vertical meningitis. In 1881, in collaboration with Warner, he presented a paper to the International Congress of Medicine in which a systematic examination of the occurrence of subcutaneous nodules in acute rheumatic fever is made. These nodules had been noticed previously, but Barlow and Warner pointed out their frequency and serious prognostic significance. They found that these nodules usually appeared only in the presence of actively progressive cardiac disease and that most cases ended fatally.

Barlow translated Raynaud's papers on "Local Asphyxia and Symmetrical Gangrene of the Extremities" from the French, and added some of his own observations on the subject, showing that intermittent hemoglobinuria and Raynaud's disease were likely to occur together.

His most important work was concerned with infantile scurvy. In 1883 he published a paper with the title "On Cases Described as 'Acute Rickets,' Which Are Probably a Combination of Scurvy and Rickets, the Scurvy Being an Essential and the Rickets a Variable Element." In 1894 he enlarged upon the same subject in the Bradshaw lecture of that year. The demonstration that scurvy could occur in infancy was not new; it had been described by Glisson in his treatise on rickets as long ago as 1651. Scurvy appears to have been a very common disease in England at that time and sometimes whole families were struck down with it, so that it was easy to recognize that the same disease was affecting adults and infants despite the greater emphasis on bony lesions among the the latter. With changes in the nation's dietary habits the disease later became less common and Glisson's account was forgotten. Liebig's analyses of foodstuffs about the middle of the nineteenth century laid the way to a scientific approach to infant feeding, and proprietary infant foods prepared by cooking mixtures of sugar, flour, and skimmed milk became increasingly popular. As a result of these advances infantile scurvy once again became more common. Möller described three cases in 1859 as "acute rickets" and his authority was such that nobody questioned this opinion for many years. In 1873 a case of scurvy in an infant was described by

Ingerslev, and in 1878 Cheadle, working at Great Ormond Street, also published an account of some cases and showed that they responded to antiscorbutic treatment with orange juice or potatoes in the same way as adults. Cheadle had been very familiar with scurvy in adults during his exploration of northwest Canada in 1863, which, no doubt, helped him to diagnose the same disease in infants when he saw it later in London. These reports, however, did not make a great impression, which is not altogether surprising, since there was at that time considerable confusion with regard to the nature of scurvy. Some authorities believed that there were different varieties, sea and land scurvy, in epidemic and endemic forms, and the cause was thought by some to be an infection, while others realized that diet was of importance.

The medical profession really became convinced of the existence of scurvy in infancy when Barlow published his paper in 1883. Here he analyzed thirty-one cases, giving exhaustive post-mortem findings in three. Adding his own cases to nineteen others which had previously been reported in the literature, many of them as cases of acute rickets, he showed that although rickets was present in some, it was by no means present in all, and that the specific lesions as shown at autopsy, namely, subperiosteal hemorrhage, thinning of cortical bone, and weakening with sometimes separation of the epiphysis, or, in the case of the ribs, backward displacement of the costal cartilage at the costochondral junction, bore no resemblance to the lesions found in rickets. He disposed of the hemorrhagic conditions as a cause of the changes found in these infants, and also ruled out congenital syphilis. He then pointed out the similarity between these cases and adult scurvy and showed that they could be cured by antiscorbutic measures. He also showed that there was invariably a history of artificial feeding on a diet containing no fresh food prior to the development of symptoms. He suggested that the disease could be prevented by giving infants over the age of 6 months some fresh food such as potato or fruit juice. Confirmatory reports from many countries followed this paper. In America in particular the disease appeared to be common, for one group of observers were able to collect over one hundred cases in a short space of time, an incidence which did not surprise Barlow, for he referred to America as "a country which rivals our own in the favour with which proprietary infant foods have been received, and in the reluctance of well-to-do mothers to suckle their offspring."

His concern to improve the standard of nutrition among children and to decrease the incidence of diseases led him to become an active member of the "Clean Milk Society" for there was, at that time, a very low standard of hygiene among those who distributed milk in large cities. Another subject on which he held very strong views was the giving of alcohol to infants and children to quiet them. He wrote several papers on the subject, pointing out the serious consequences of the frequent administration of even small amounts of spirits.

Early in his life he was a strong believer in the cause of temperance, and the illness and suffering he saw in his hospital practice resulting from overindulgence in alcohol can only have reinforced this conviction. Later he modified this view, and while still condemning the use of spirits, he thought it permissible to drink wine—although never to excess.

It is possible that had he never married, Barlow would have continued his scientific researches throughout his life, but the responsibility of providing for a growing family and the expansion of his private and consulting practice left him no time for scientific work. However, he used to recount somewhat ruefully a rebuke of Dr. Jonathan Hutchinson that he was like the man in Proverbs who "roasteth not that which he taketh in the chase."

By the end of the nineteenth century he was recognized as one of the leading physicians in England and had many honors bestowed upon him. He was appointed Physician Extraordinary to Queen Victoria in 1889 and continued to hold court appointments under Edward VII and George V. In 1900 he was made a baronet; in 1909 he was elected a Fellow of the Royal Society in recognition of his work on infantile scurvy; and in 1910 he became president of the Royal College of Physicians, being re-elected to this office for the next four years.

Although he left his mark in the scientific field of medicine, his contemporaries and those who worked under him would perhaps note his personal qualities as even more important. He had a gift which enabled him to make direct contact with people, inspiring their confidence and often their lasting devotion. Dr. L. P. Hartley wrote in his book *Behind the Night Bell* in 1938, "Barlow . . . had a sort of intuitive flair for diagnosis. He had more than that he had the knack of saying always the kind thing. The Old Queen did well when she chose him as one of her advisors. He was very blunt; he was very rugged—he came from the North Country; he was fundamentally honest. It is forty years since I last spoke to him, but I love him today as I loved him forty years ago. I still feel I owe him more than I can ever repay. He, more than anybody else taught me the merits of Humanism applied to Medicine; and he did it not by any deliberately spoken word but by being just himself."

Religion played a very important part in his life. He had been brought up as a Wesleyan and remained faithful to this branch of the Church, but after coming to London, Frederic Denison Maurice,* and Page Roberts† had much influence on his religious views. Like many nonconformists he felt that the sermon was by far the most important part of the Divine Service, and in his declining years he still liked to have a sermon read to him, especially on a Sunday, those of Jowett and Robertson being favorites. Apart from these, biography and reflections such as the *Colloquies of Erasmus* were his favorite reading.

He had many interests outside medicine, and when, after he had reached the age of 80, his practice diminished this left him with more time to devote to art, literature, music, and archaeology. Each year, after the

*Founder of the Working Men's College in London.

†Dean of Salisbury.

death of his wife, until World War II, he made a trip to the Continent and visited places of historical or archaeological interest, seldom spending more than a night or two in one place; nevertheless he always remembered practically everything he had seen. His companion on one of these journeys was his great friend Charles Brent, Bishop of Western New York, formerly first Bishop of the Philippines, and he was with Bishop Brent when he died in Lausanne in 1929.

His youthful spirit at the age of 88 is illustrated by a remark he made after visiting a Jewish friend in Germany who, although many years younger, had suffered much at the hands of the Nazis. "Dear me," he said, "when my time comes, I hope I shall mellow as gracefully as that." One might say that his wish was granted, for he retained his interests and much of his physical activity until his death in January, 1945, at the age of 99.

Andrew Barlow

Comments on Current Literature

HEREDITARY HYPERCHOLESTEROLEMIC XANTHOMATOSIS

THE role of cholesterol as a factor in the development of atheroma has been studied extensively. Not infrequently hypercholesterolemia is observed in patients with ischemic heart disease, especially in those under 50 years of age, and is known to occur in association with coronary atheroma in patients with diabetes mellitus or with myxedema. J. C. Leonard[1] of the National Heart Hospital in London states in a recent article that "the relationship between a raised serum-cholesterol level and atheroma is most clearly seen in hereditary hypercholesterolaemic xanthomatosis." Observations made on patients with this interesting clinical syndrome are summarized by Leonard in *Lancet*, issue of Dec. 15, 1956. In this group of patients, the remarkable association of hypercholesterolemia with the occurrence of ischemic heart disease at an early age offered opportunity for study of the etiologic relationship between elevated cholesterol levels in the blood and the development of atheroma, particularly in the younger age range.

Over a period of years, eleven families with hypercholesterolemia and xanthomatosis were studied, and in ten of the eleven, contact with the family was first made because one of their number developed ischemic heart disease. In the eleven families, twenty-nine patients with hypercholesterolemia were studied: in ten patients with hypercholesterolemia alone, the mean age was 31 years, range 9 to 56 years; in nineteen patients with clinical evidence of xanthomatosis, the mean age was 46 years, range 30 to 70. Patients with clinical manifestations of the disease showed xanthelasma around the eyes and on the eyelids, xanthoma tuberosum and tendinosum, nodular yellowish orange elevations on the skin, sometimes seen on the volar surfaces of the hands, but commonly occurring on the extensor surfaces of the arms, and on the elbows, knees, and buttocks. The tendon lesions consist in subcutaneous nodes, firm and attached to the extensor tendons of the fingers at the level of the metacarpophalangeal joints, to the Achilles tendons, and less commonly to other tendons of the upper and lower limbs. Apparently no disability results from their presence unless there is interference with the neighboring joint. In this group of patients described by Leonard, atheroma developed in the cardiovascular system at an early age and to a more marked degree than in the general population. Occasionally in young adults with this disease, corneal arcus is seen. Patients with hypercholesterolemia alone have been classified as showing an atypical or abortive form of the disease (formes frustes), a classification which the author considers misleading since it implies a disease present in mild form only. Leonard's studies are in agreement with those of Piper and Orrild,[2] who pointed out that although patients with hypercholesterolemia alone may not show clinical manifestations of xanthomatosis in younger life, at least 80 per cent of them are destined to develop frank xanthomatosis later on.

The clinical details of Leonard's studies are given in tabular form. In one family eight members showed elevated total serum cholesterol levels. These eight persons ranged in age from 11 to 70 years: one, aged 70, died as the result of an aortic aneurysm; in another, aged 70 years, the cause of death was given as rupture of an aortic aneurysm; a brother, 56 years, had no symptoms; a son, 43 years of age, had xanthoma tuberosum and tendinosum and renal calculi, and was known to have had ischemic heart disease for a period of

four years. Another son, 35 years of age, had xanthoma tendinosum and renal calculus, and a daughter, 38 years, xanthoma tendinosum. A niece, 26 years of age, and two granddaughters, aged 11 and 12 years, were free from clinical manifestations. A brother, aged 50 years, who was not available for blood studies, died three years later, the cause of death being given as ischemic heart disease.

Another remarkable family study included a 47-year-old patient who had xanthelasma and ischemic heart disease for a period of eleven years. His brother, 51 years, died of ischemic heart disease before serum cholesterol studies could be accomplished. A sister, 45 years, had xanthelasma and was known to have had ischemic heart disease for one year; another sister, 43 years of age, had suffered from ischemic heart disease and intermittent claudication for a period of three years. The consistent association of high cholesterol levels in the blood in these patients with xanthomatoses and the occurrence of ischemic heart disease are impressive. In the case of several of these families, excellent genetic studies were possible, and the pedigree tabulations were compatible with the view that this inborn error of lipid metabolism is inherited as a Mendelian dominant which is variable in its expression.[2, 3] Hypercholesterolemia rather than xanthomatosis is considered the principal manifestation of the inherited factor. While there has been some suggestion that the more severe manifestations may be associated with the homozygous state, verification of this suggestive evidence has not been possible. Some individuals with high blood levels of cholesterol are able to live a normal span. In general, however, ischemic heart disease tends to occur at a much earlier age. In thirteen patients followed carefully in the present series, the average onset of cardiovascular symptoms was at 43 years of age. According to Leonard, the prognosis depends entirely upon the degree of predisposition to the development of atheroma, hypercholesterolemia per se not being the deciding factor.

In a section on treatment, Leonard[1] discusses briefly the general methods of therapy which have been employed. "The object of treatment is to reduce the serum-cholesterol to normal; skin xanthomata may then regress, but tendon lesions are rarely, if ever, affected. If the serum-cholesterol is maintained at a normal level, the liability to develop ischaemic heart-disease may be minimised." Dietary restriction has been recommended for some years, with conflicting reports as to its value. One patient in the series presently reported was placed on a low-fat diet without satisfactory alteration of the serum cholesterol level. A number of recent biochemical and nutritional investigations has shown that the body normally synthesizes considerable amounts of cholesterol from acetate, pyruvate, and other products of metabolism.[4] Even a cholesterol-free diet could not be expected, then, to effect a significant change in the over-all cholesterol metabolism. In fact, extensive studies in adults have disclosed that the serum cholesterol level is essentially independent of the cholesterol intake. The problem is being resolved currently into one not of restriction of dietary cholesterol, but of prevention of cholesterol absorption in the intestine and from the enterohepatic system. In 1955 Malmros and Wigand[5] treated eight patients having various manifestations of hereditary xanthomatosis by means of a diet rich in corn oil, with subsequent fall in cholesterol level and improvement in clinical symptoms. Four patients in the series described by Leonard were treated in this manner.

Corn oil has been shown to contain a plant sterol, beta-sitosterol, which is present in soybean, cotton seed, corn, etc. While plant sitosterols are considered chemical analogues of animal cholesterol, very little of this type of sterol is absorbed by the human body, and any small amount absorbed is excreted rapidly. In addition, sitosterols apparently are capable of blocking the absorption of

cholesterol, since it appears that in the gastrointestinal tract, sitosterols form with cholesterol a 50:50 mixed crystal which is relatively insoluble; cholesterol is therefore not available for absorption. Because of the nature of the enterohepatic transport, any substance which blocks intestinal absorption will also lessen or prevent reabsorption of endogenous cholesterol.[6, 7] Recently Levkoff and Knode[7] have found sitosterol of value in the treatment of two children with familial hypercholesterolemia.

Leonard[1] also discusses the use of heparin as a means of treatment in patients with hereditary xanthomatosis, since these patients have been found to have, in addition to cholesterolemia, increased amounts of certain classes of lipoproteins. However, while heparin does offer "a possible method of lowering the serum-cholesterol level, . . . the treatment is expensive and not without risk, and its use should probably be confined to those (selected) patients who have developed ischaemic heart disease."[1]

Investigations pertinent to lipid and cholesterol metabolism are under way in a number of centers: improvement in the laboratory methods for the detection and study of these substances; the nature and importance of the essential fatty acids; the effects of nicotinic acid and related complexes; possible metabolic regulatory mechanisms in relation to cholesterol and lipoproteins; the discovery of a plasma lipid mobilizing factor possibly of significance in man, etc.[8] The possibility of preventive measures and the avoidance of serious complications by early treatment of patients with essential hypercholesterolemia is a stimulating thought for the physician interested in preventive medicine.

RUSSELL J. BLATTNER

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Correspondence

To the Editor: Concerning Aminophylline

The publication of various articles the past year or so concerning the possible toxic effects of aminophylline in asthmatic children has been very pointedly summarized in the article by Veum and Schwartz.[7] These reports have led to a lessened use and may even lead to the abandonment by some of what we consider to be a potent and relatively safe antiasthmatic drug.

Our experience with this medicament covers a period of more than twenty years, during which we have not had a single death attributed directly or indirectly to aminophylline or any serious toxic reaction. The individual susceptibility to the toxic effects of this drug, like any other drug in an allergic individual, is largely unpredictable. It was early observed that the most common toxic effects, whether the drug was administered orally, intramuscularly, or intravenously, are nausea and/or vomiting. For this reason, we did not administer aminophylline to patients who were already nauseated or vomiting until this condition was relieved. If the patient did not have these symptoms at the time of first administering the drug, it was discontinued at their first appearance. In such cases, it was often possible to use the drug in smaller doses after these symptoms had disappeared. If the patient were dehydrated and not nauseated or vomiting, aminophylline was given slowly intravenously, well diluted, with plenty of fluid, preferably 5 per cent dextrose. Central nervous system symptoms in our patients have been conspicuous by their absence. The urines were studied only in hospitalized patients and albuminuria was never observed as a highly significant finding.

We are not convinced that the side reactions reported were due to this drug per se. There are a number of commercially available suppositories and oral preparations which combine aminophylline with ephedrine and one of the barbiturates. Gardner and associates[2] have pointed out that in white rats there is a fourfold increase in the toxicity of ephedrine by the inclusion of a small dose of aminophylline and a doubling of the toxicity of aminophylline by the administration of a relatively small dose of ephedrine. While this may not be true in man, it very definitely appears that the combination of these drugs in oral tablets is highly effective and, to some degree, the stimulating effects can be reduced by a combination with a barbiturate. When such preparations are used, the physician is often hard pressed to determine which of the ingredients is responsible for the toxic reactions. Furthermore, a number of disagreeable effects attributed to the aminophylline might conceivably be due to the underlying disease process.

For many years, the literature was distinguished by its absence of references to aminophylline toxicity in children. In 1953 Berkowitz and associates[1] noted "side reactions" to aminophylline in 11.5 per cent of eighty asthmatic children. They regarded these reactions for reasons discussed in their publication as probably evidence of minor allergic disturbances. Rounds,[6] in 1954, presented comprehensive data concerning aminophylline toxicity in 6 children. We agree with him that toxicity resulted from overdosage rather than from individual sensitivity or idiosyncrasy.

In the article under consideration,[7] Case 1 is of interest because of the statement that aminophylline was ordered every 6 hours in a dose of 0.250 Gm. despite the fact that the child was vomiting and obviously dehydrating. The dangers of overdosage appear to be as frequent, from reported cases, in hospitalized patients as it is with those treated at home. The reason for this seems quite clear. Too often in a hospital setting, fixed orders are written and often not amended as the patient's condition warrants. Although the index of suspicion points to aminophylline toxicity in Case 1, we believe that

the evidence presented is only presumptive. There is a distinct possibility that a number of viral infectious diseases could have or may have produced a similar clinical picture. It is, however, of secondary importance to dispute whether aminophylline is the sole cause of the patient's symptomatology. Rather, it would seem reasonable and practical that any asthmatic patient, who presents even with a moderate degree of nausea or vomiting, should not receive aminophylline until this state has been corrected. To administer aminophylline under such circumstances would merely complicate determining which factor or combination of factors is responsible for the protracted vomiting. Furthermore, aminophylline should be given with caution to patients in moderate or severe degrees of dehydration and, as stated above, the patients should at the same time be well hydrated.

The dose as recommended by one of us[3] for intravenous use is quite satisfactory but for rectal administration the dose could easily be twice as much. The schedule suggested by White and Daeschner[8] is somewhat less conservative but probably more in line with the therapeutic needs. This is as follows: 3.5 mg. per kilogram for intramuscular or intravenous use; 5 mg. per kilogram orally and 7 mg. per kilogram by rectal suppositories. We now, however, practically never use aminophylline intramuscularly because it is exceedingly painful, and this route is almost always unnecessary.

We believe it should be emphasized that because of the variation in the individual patient's requirements, any rule of dosage is only arbitrary. The frequency of administration of the drug should be individualized. We usually advise that the suppositories not be inserted oftener than every 6 to 8 hours.

Unfortunately, because of the way in which suppositories are made, one cannot be sure that the active ingredient is uniformly dispersed through the suppository. For this reason, it is not accurate to prescribe one-half or one-quarter of a suppository because there is no certainty just how much of the aminophylline would be in the portion used. In doses below the half-strength suppository, one must prescribe powders of aminophylline in the required amount to be injected rectally with a small amount of water. A proportionate amount of an ampule of aminophylline in aqueous solution may also be used instead of the powder.*

It should further be mentioned that, if there is an absolute contraindication to the administration of aminophylline, intramuscular hydrocortisone is highly satisfactory. We commonly use 50 to 75 mg. in early infancy and 75 to 125 mg. in older children. Under such circumstances the patient should be protected by an antibiotic and potassium administered if there is evidence of hypokalemia or this drug is continued. There is no danger of initial high doses with this drug and the evidence presented by Hellman and associates[4] indicates that 70 to 80 per cent of the hormone is eliminated in the urine within twenty-four hours. It is, also, not at all improbable that, if future experience confirms the present favorable results, treatment with corticosteroids or their analogues will be the method of choice rather than aminophylline in status asthmaticus.

JEROME GLASER, M.D.
BERNARD A. BERMAN, M.D.

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*Since this letter was written it has been learned that while in some instances the manufacturing process does not distribute the active ingredient equally through the suppository, in other instances it does. If one desires to use fractions of suppositories it is advisable to have information concerning this from the maker of the specific preparation one would like to employ.

News and Notes

The following were certified by the **American Board of Pediatrics**, at the examination held in Washington, D. C., April 5, 6, and 7, 1957.

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Dr. Robert L. S. Baird, 5048 13th St., N.E., Washington 17, D. C.

Dr. Rela Bartfeld, 226 W. 108th St., New York 25, N. Y.

Dr. Howard Elsworth Baughman, Jr., 1510 Coles Blvd., Portsmouth, Ohio.

Dr. Bernard A. Berman, 350 Beacon St., Boston 16, Mass.

Dr. Mary E. Bradford, 181 Laurel Ave., Northport, N. Y.

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Dr. Malcolm Alexander Holliday, 1433 Denniston Ave., Pittsburgh 17, Pa.

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Dr. Joseph Moses Koreen, 399 Riverside Dr., Ottawa, Canada.

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Dr. Joanne E. Mertz, The Burns Clinic, Michigan St., Petoskey, Mich.

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Dr. Edward Silliman Sherwood, 4 Hillside Rd., Rt. 9, New Brunswick, N. J.

Dr. Dazelle Dean Simpson, 823 N.W. 3rd Ave., Miami 36, Fla.

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Dr. Ned Willits Smull, 411 Nichols Rd., Kansas City 12, Mo.

Dr. Alvin A. Stambler, 6941 Reisterstown Rd., Baltimore 15, Md.

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Dr. G. Earl Trevathan, 119 N. Woodlawn, Greenville, N. C.

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Dr. Richmond Lee Walton, 39 Stonybrook Rd., Stratford, Conn.

Dr. Richard Jerome Waters, Carrington Rd., Bethany, Conn.

Dr. Charles Francis Whitten, 2538 Glynn Ct., Detroit 6, Mich.

Dr. William Cobb Wiswall, 8 Richards Rd., Lynnfield Center, Mass.

Special Foreign Certificate:

Dr. Amparo C. Adiao, 86 Amity St., Brooklyn 1, N. Y.

The following listed diplomate was certified at New Orleans, La., on Feb. 22, 1957, and will receive a regular certificate (he was not eligible to receive this certificate until April 1, 1957):

Dr. James Fairly Alison, Jr., 718 Alabama Ave., Selma, Ala.

The following pediatricians were certified in Pediatric Allergy following an examination held in Washington, D. C., on March 31, 1957:

Dr. Van Vleck Chambers, 380 Susquehanna Rd., Rochester 18, N. Y.

Dr. Lloyd Vernon Crawford, 2448 Poplar, Memphis, Tenn.

Dr. Gilbert Lanoff, 2263 E. 95th St., Chicago, Ill.

Dr. Virginia Catherine Lent, 285 N. Franklin St., Hempstead, N. Y.

Dr. Meyer B. Marks, 311 Lincoln Rd., Miami Beach, Fla.

Dr. Thomas Lothian Nelson, Box 218, Eldridge, Calif.

To stimulate an interest in clinical investigation and accurate reporting of pediatric problems, the **New England Pediatric Society** is offering an award of $200 for the best paper submitted by an intern, resident, or fellow, who is connected with a teaching hospital or medical school in the New England area. The paper should deal with one or more pediatric cases, of special interest or significance, with appropriate supporting literature, and discussion. The winner will be announced at the first meeting of the Society in the fall, and the paper will be submitted for publication in the *New England Journal of Medicine*. Papers should be submitted to Dr. Harry Shwachman, Secretary, New England Pediatric Society, 300 Longwood Ave., Boston, Mass., by June 30, 1957.

Under the auspices of the *American Academy of Pediatrics*, a special registry, devoted to Pediatric Pathology, is to be established as one of the components of the **American Registry of Pathology of the Armed Forces Institute of Pathology.** The success of other component registries in collecting adequate source material for the study of rare and unusual disease processes in several branches of medicine has prompted the Armed Forces Institute of Pathology to devote a special section to the pathology of diseases of children. The advantages of this procedure are many. Making available the extensive facilities of the Armed Forces Institute can add greatly to the thoroughness with which specimens can be processed. Collection of

large numbers of specimens yields statistical data not obtainable otherwise. Accessibility for the profession at large to data and material from diverse sources facilitates the study of topics of special interest, especially for individuals with special techniques.

The advantages of a special Registry of Pediatric Pathology accrue from the special character of pathology as seen in children, where growth processes must always be considered along with disease, and where disturbances of growth render this field of pathology distinctive from other fields. The Registry of Pediatric Pathology will limit its material only with respect to the age group involved. Adequate cataloguing, maintenance of records, and availability of material are primary objectives in the procedure. In addition, a consultation service will be provided for all pathologists, similar to that offered by the other component registries. Leading authorities in pediatric pathology in this country and abroad will thus be on call for questions in their special fields of interest. The material will also be made available for teaching purposes, and it is hoped that in the future, the Registry may provide a position for training in pediatric pathology. The support of all pathologists and pediatricians, therefore, is needed to ensure the success of this new division. All inquiries concerning it should be addressed to the Registry of Pathology at the Armed Forces Institute of Pathology. Any interested physician is invited to visit the Registry at his convenience at Walter Reed Medical Center, 6825 16th Street, N.W., Washington 25, D. C.

The Committee on Pediatric Pathology of the American Academy of Pediatrics consists of Drs. Sidney Farber, Boston, Chairman; Edith Potter, Chicago; Irving Wolman, Philadelphia; William B. Kiesewetter, Pittsburgh; George H. Fetterman, Pittsburgh; Robert S. Cleland, Los Angeles; Major Daniel Stowens, MC, of the Armed Forces Institute of Pathology is Secretary of the Committee.

Among the twenty-five grants made by the **John and Mary R. Markle Foundation** in its Medical Faculty Aid Program this year, three were in the field of pediatrics. The grants are for $6,000 a year for five years. The pediatric grants were made to:

Robert E. Carter, M.D., University of Chicago

Frank Falkner, M.D., University of Louisville

Donald E. Pickering, M.D., University of Oregon

Since the start of the program ten years ago, 206 physicians have received help from the Foundation, twenty-five have become professors and heads of departments in different medical schools, and fifty-one hold associate professorships. The twenty-five appointed this year were selected from fifty-seven candidates.

On April 12 and 13, 1957, an *Institute on Newborn and Premature Care* was held in Winnipeg, Canada, under the auspices of the **Department of Pediatrics** of the **University of Manitoba.** Dr. Howell Wright of Chicago was the guest speaker. The two-day program participated in by members of the medical school faculty covered such topics as normal feeding, the effect of maternal disease on the infant, nursery infection, resuscitation, and erythroblastosis.

Books

The Mentally Retarded Patient. Harold Michal-Smith, Philadelphia. 1956. J. B. Lippincott Co. 203 pages.

This little volume skips lightly over the problems of mental retardation with only an occasional dip below the surface. Written ostensibly as a "guide for the physician" in understanding the psychological aspects of the mentally retarded patient, its content is, for the most part, superficial and unsatisfying, its style chatty and repetitious.

The book has nine chapters, a selected bibliography, and an appended list of state and private institutions caring for the mentally retarded. The first five chapters attempt to describe the problem, discussing the role of the physician, brain impairment, learning and emotional factors, classification of mental retardation (written by Lawrence B. Slobody and associates), attitudes toward prevention and etiology and the psychological situation. These chapters, except that on classification, are oversimplified, replete with vague generalizations and unfortunate errors of fact. It is stated, for example, that (p. 14) "at present infectious diseases of the embryo and of the mother during pregnancy are believed to play a *large* part in causing brain damage''; and again, on page 15, "as a rule, the neurological signs for diagnosis of lesions of the central nervous system are considered by physicians to be first and foremost the Babinski sign and paralysis of the cranial nerves." One looks in vain for a description of the large group of mentally retarded children who do not show classical neurological signs and for a description of the emotional consequences of retardation in the child.

In the last four chapters, Dr. Michal-Smith appears to be on more familiar ground and writes more like the authority he is. These chapters include problems of family adjustment, education, and vocational prognosis. In each of these chapters there is a description of specific research conducted by the author and his associates; specialized techniques in group therapy with retarded adolescents, a home training program for retarded children, and a study of the personality traits which make for maximum employability of the mentally retarded patient. These chapters are authoritative and informative. It is unfortunate that the first half of this book is not.

A. A. S.

Treatment of the Child in Emotional Conflict. Hyman S. Lippman, M.D., Minneapolis, 1956, The Blakiston Division, McGraw-Hill Book Company, Inc., 291 pages. Price $6.00.

In his introduction the author states that the methods of therapy described in his book are based largely on the principles of therapy received during his psychoanalytic training in child analysis under Anna Freud and August Aichhorn, presumably in the twenties. Dr. Lippman adheres to his orthodoxy unflinchingly. "Child analysis," he writes, "has profoundly influenced the therapy of disturbed children by methods other than analysis." It represents "the ideal form of therapy for the deeply conflicted child." It is his thesis that most pediatricians have not had the special training required for treating the emotionally disturbed child. Indeed he considers it unsafe for the pediatrician to handle these cases.

The author's management of an emotionally disturbed child is elaborate. The parents are first interviewed, together, by the case worker, then separately. The case worker treats the parents; a therapist, presumably the child psychiatrist, treats the child. A psychologist and group therapist are also involved. There are frequent conferences about the patient's progress. Treatment goes on for years.

Such a therapeutic regimen hardly seems practical. The trained personnel are not available to treat any sizeable number of patients. The expense involved is beyond

the pocketbook of most individuals or communities. There is also the question of time which, perhaps, could be spent in more productive ways. Moreover there are no data to indicate that these elaborate therapeutic techniques are of any value whatsoever.

Illustrative of the author's type of thinking is the chapter headed "The Child Who Withdraws Into Convulsive Seizures." The chapter opens with the following statement: "The epileptic convulsion has been thought to represent a desperate attempt by the ego to escape from an unbearable traumatic situation." Though the author does not specifically state that he agrees with this statement, he goes on to describe a child who had repeated convulsions since the age of 7 months associated with breath-holding. He concludes that this baby "may have needed to escape through her convulsions from an unbearable reality."

The Physician-Writer's Book. R. M. Hewitt, M.D., Philadelphia, 1957, W. B. Saunders Co., 415 pages. Price $9.00.

To those who have the urge to contribute to medical literature we recommend an investment of nine dollars in this book. The subtitle is "Tricks of the Trade of Medical Writing." The author as chief of the Section on Publication of the Mayo Clinic had many years of experience in helping physicians prepare their books and papers for publication. Dr. Hewitt's message is first to have something to say, and then to say it in as few words as possible with due respect for clarity. The book goes into many details of how this can be accomplished. If it could be made compulsory reading for embryonic medical authors it would be a godsend to the editors of medical journals.

Many times over the years a remark by the late Thomas B. Cooley—one of the most scholarly writers American pediatrics has produced—has flashed across the reviewer's mind. Once when the subject of premedical training was under discussion, Cooley remarked that he considered three things essential: first, English; second, more English; third, more, more English. Particularly to those who lacked the second and third of these essentials in their education, Dr. Hewitt's text should be of great help and service.

B. S. V.

Counseling and Psychotherapy With the Mentally Retarded. Edited by C. L. Stacey and M. F. DeMartino, Glencoe, Ill., 1957, The Free Press, 478 pages. Price $7.50.

A collection of papers or sections of books which have appeared in recent years, presenting discussions of therapeutic work with the mentally retarded child. It includes play, speech, group and occupational therapy, and a section on the important subject of counseling with parents. With the increasing interest in recent years in the retarded child from both the medical and psychological viewpoints, the book collection gives an excellent picture of the present status of the psychotherapeutic methods in use. The book is chiefly of interest to individuals working with retarded children. Much of the methods in use must be regarded as experimental so far as end results are concerned. That a need for such a book is indicated for those working with retarded children is in itself highly promising for the future.

Six Children. Estelle J. Foote, M.D., Springfield, Ill., 1956, Charles C Thomas, 317 pages. Price $5.50.

Dr. Foote, formerly psychiatrist in charge of the Traveling School Clinic in Massachusetts, has grouped the children studied at the clinic into six main categories or divisions: the quick thinking child; the slow thinking child; the child with a brain injury; the child with emotional maladjustment; the child with an unusual cultural background; and the child with unusual training. Each forms the basis of a chapter with illustrative case histories. In a final section forms and charts for history taking, examinations, and record keeping are discussed. The book is interesting and the reader is not overwhelmed by psychiatric jargon.

Muscle Testing, ed. 2. Lucille Daniels, M.A., Marian Williams, Ph.D., and Catherine Worthingham, Ph.D., Philadelphia, 1956, W. B. Saunders Co., 176 pages. Price $4.00.

A second revised and enlarged edition of the manual first issued ten years ago. The text is practical and well illustrated.

Editor's Column

AMINOPHYLLINE TOXICITY

AN INCREASING number of reports of poisoning due to aminophylline have appeared in recent pediatric literature. This issue contains two discussions, one a paper by Dr. Soifer (page 657) and the other a letter in Correspondence (page 782) from Drs. Glaser and Berman. Both stress the dangers of summation effects when aminophylline is combined with other agents such as ephedrine. Obviously considerable confusion exists as to dosage and method of administration.

Dr. Soifer's paper presents a discussion of the pharmacological action which might well serve as an example for other authors, as there is no question but that too many therapeutic agents are prescribed in which the physician's knowledge is limited to conditions for which its use is recommended.

Familiarity with labeling, which unfortunately often fails to give the dosage schedule for children of varying size, is a requisite for drug therapy if physicians are to recommend proper doses through professional prescription channels. The dosage schedule for aminophylline recommended by Dr. Soifer is safe and probably usually adequate.

OPHTHALMIA NEONATORUM PROPHYLAXIS

A RECENT ruling of the Health Department of the City of New York repealing the section of the Sanitary Code relating to the specific prophylaxis of ophthalmia neonatorum is of great medical interest. To quote from the announcement made in January of this year:

> Gonorrheal ophthalmia neonatorum used to be a common and serious disease in the days when antibiotics were not known and when hygiene and sanitation were not as highly developed as they are today. The Credé method of prophylaxis (instillation of a 1 per cent silver nitrate solution in the eyes of newborn infants) was a great step forward in control, and many health departments made such prophylaxis a requirement. For many years this mode of prophylaxis was required in the sanitary code of the City of New York.
>
> In recent years modifications have been introduced in the sanitary code of this city. In general, these changes have permitted the use of other effective agents in the prophylaxis of ophthalmia neonatorum.
>
> The time has come for a reappraisal of the entire matter. Gonorrheal ophthalmia is a rare disease in this city. Even when it does occur it is readily diagnosed and treated with penicillin or other antibiotics. The Board of Health has given thought to this

question and has decided that the need for specific prophylaxis of ophthalmia neonatorum no longer exists. Accordingly, at a meeting held on December 21, 1956, a resolution was adopted repealing section 104 of the sanitary code. This removes the requirement that prophylactic measures of any sort need be taken at the birth of a child for the prevention of ophthalmia neonatorum.

Some five years ago (September, 1952) the JOURNAL editorially urged that the use of the Credé method of prophylaxis cease to be a matter of statute and of medical subservience to tradition. In many cities the use of antibiotics for prophylaxis has become permissible, and the experience has been satisfactory. New York City has gone a step further and specific prophylaxis of any kind is no longer required. There is evidence that simple flushing of the eyes of the newborn infant with sterile water is the most important factor in prophylaxis.

While in full agreement with the New York City ruling, we do not think there should be a rush for a similar change in the law in every community or state. Nothing would be lost if antibiotic prophylaxis is continued generally for a few more years. The Health Department of New York City is one of the finest and most progressive in the world. Its reports can be relied upon. It is in unusual close touch with and supervises the obstetrical clinics, and has the respect and cooperation of the physicians in New York. If after a few years it has been demonstrated by their experience under the new ruling that no increase in ophthalmia has occurred, important evidence would be available to support a similar change in the law in other communities and states. While we believe that New York City is on the right track, there is nothing urgent involved. It would be best to regard the change in the New York City law as an important scientific experiment to be watched for a few years with a great deal of interest.

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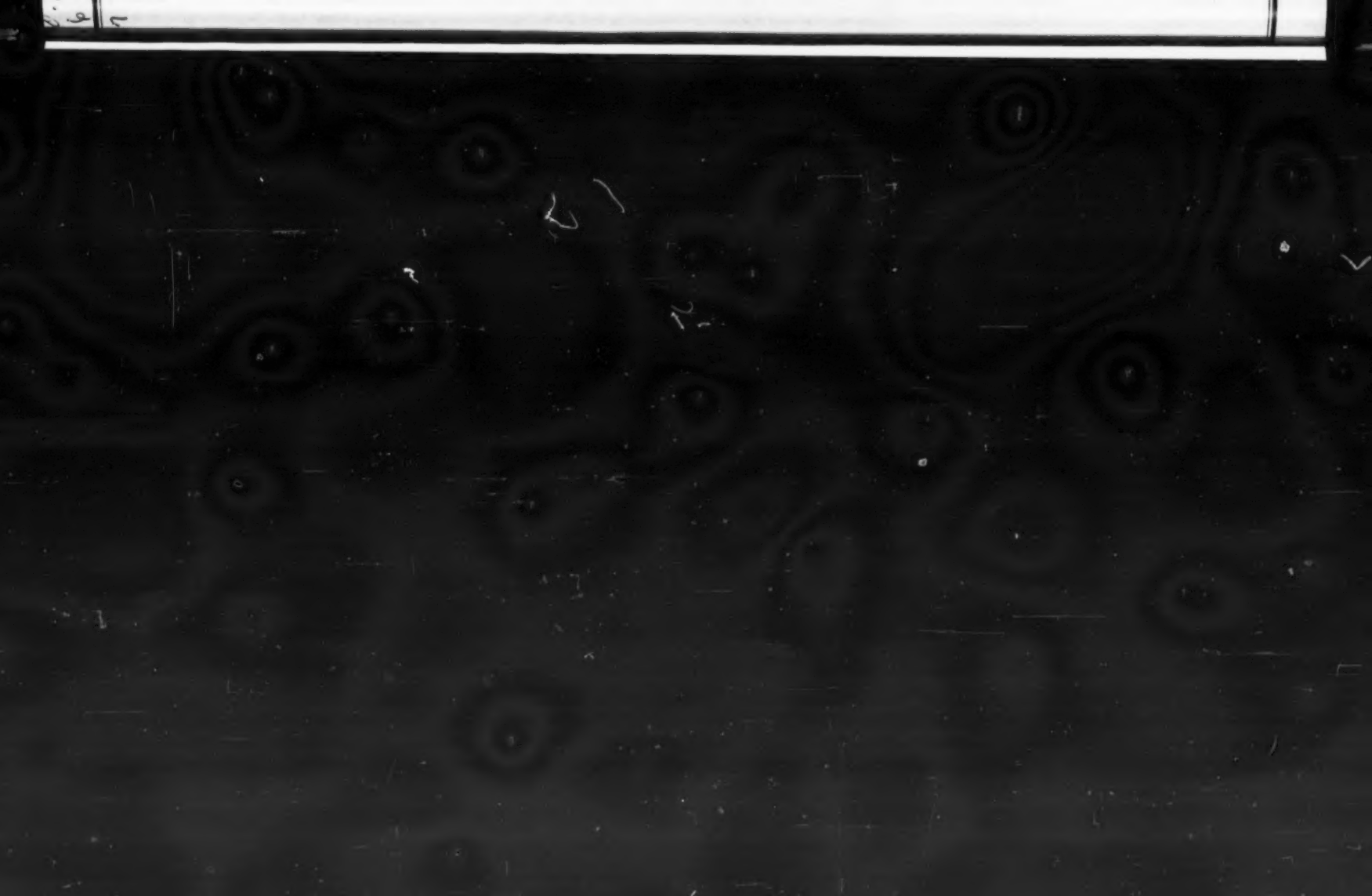

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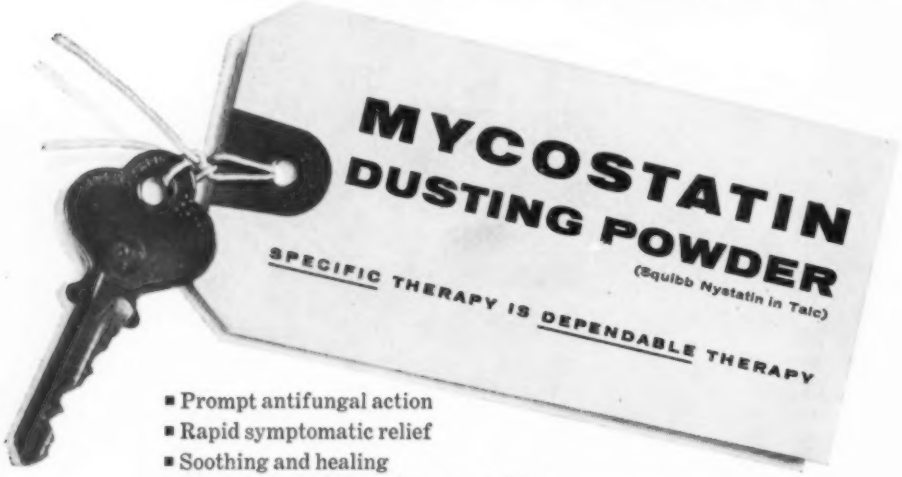

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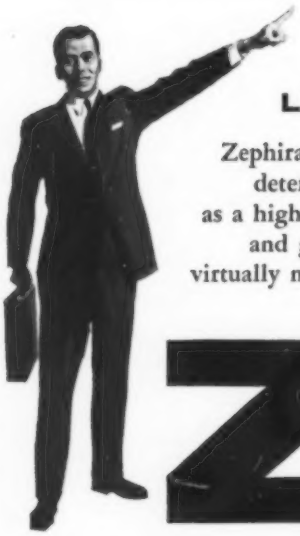

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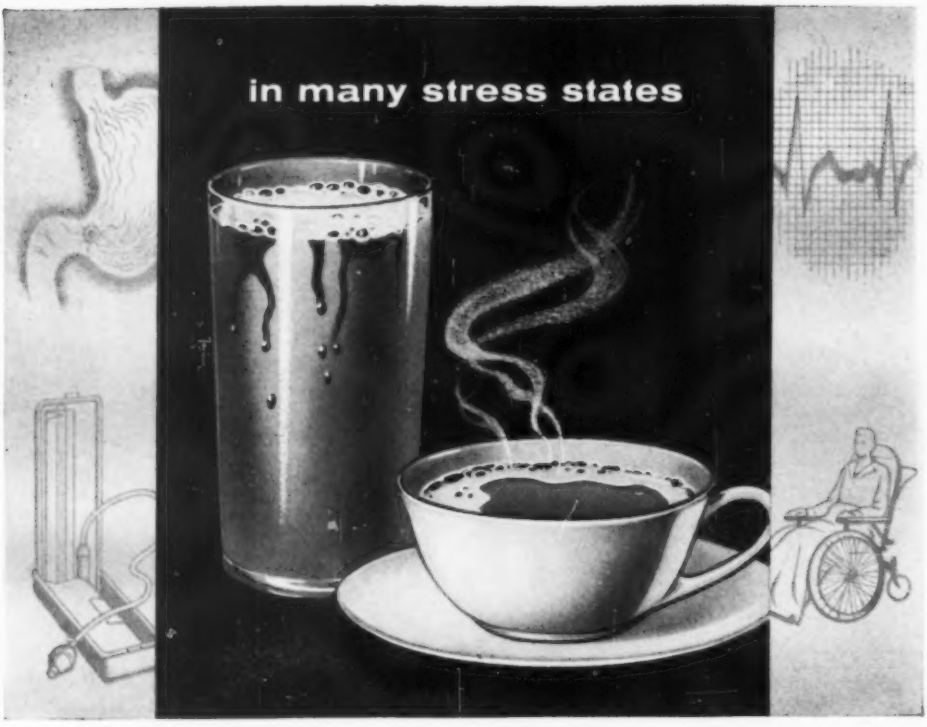

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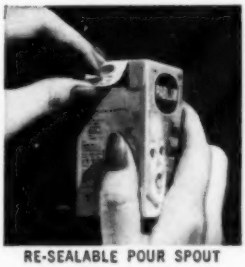

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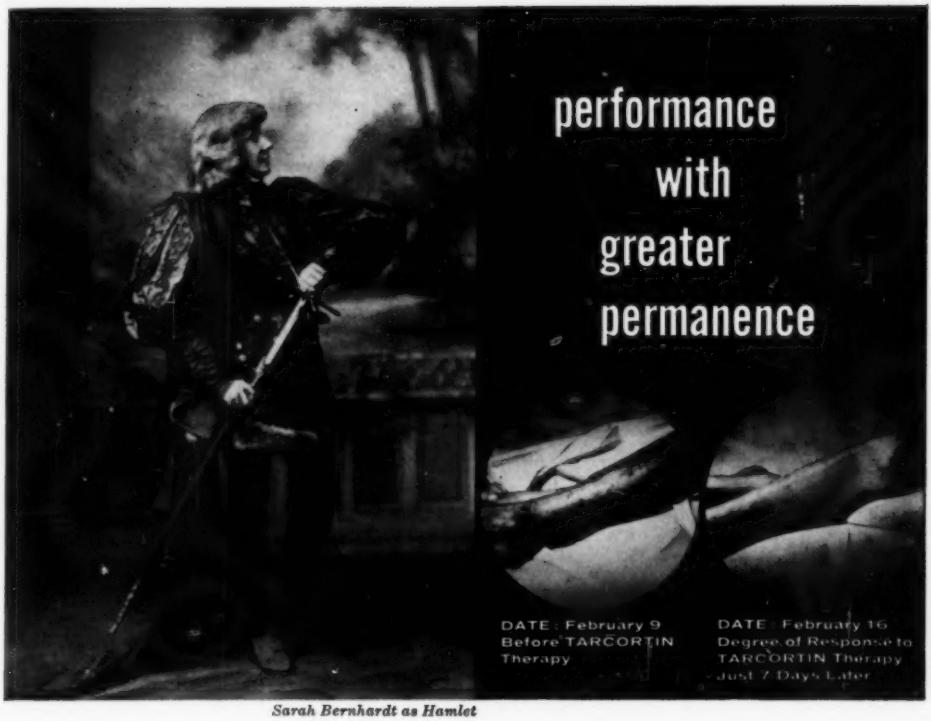

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BIBLIOGRAPHY:
(1) Welsh, A. L., and Ede, M.: Hydrocortisone Ointments: Their Rational Use in Dermatology, Ohio State M. J. 50:837 (Sept.) 1954. (2) Clyman, S. G.: The Comparative Effects of Hydrocortisone and Hydrocortisone-Coal Tar Extract (Tarcortin) Creams in Atopic Dermatitis. Postgrad. Med. (Mar.) 1957. (3) Abrams, B. P., and Shaw, C.: Atopic Dermatitis Treated with Tar-Steroid (Tarcortin) Cream—A Case Report, Clin. Med. 3:839 (Sept.) 1956.

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for infections
in children →

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DESCRIPTION:

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DOSAGE:

Children:	teaspoonfuls every 12 hours
20 lbs	1
40 lbs	1½
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80 lbs	3
Adults:	4

CAUTION:
The usual precautions in sulfonamide therapy should be observed.

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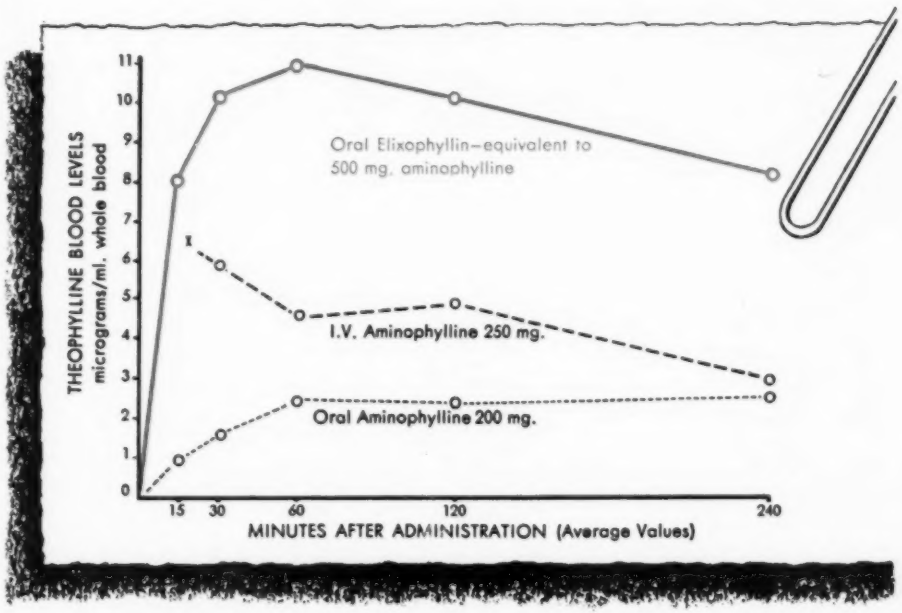

Adult dose for severe attacks is a wineglassful (75 cc. or 5 tbsp. containing theophylline equivalent to 500 mg. aminophylline). Well tolerated.

Children's dosage: 0.375 (⅜) cc. per lb. body weight.

Elixophyllin data—Schluger, J., et al.: Am. J. M. Sci. 233:296, 1957; other data—Waxler, S. H. & Shack, J. A.: J.A.M.A. 143:736, 1950.

ELIXOPHYLLIN

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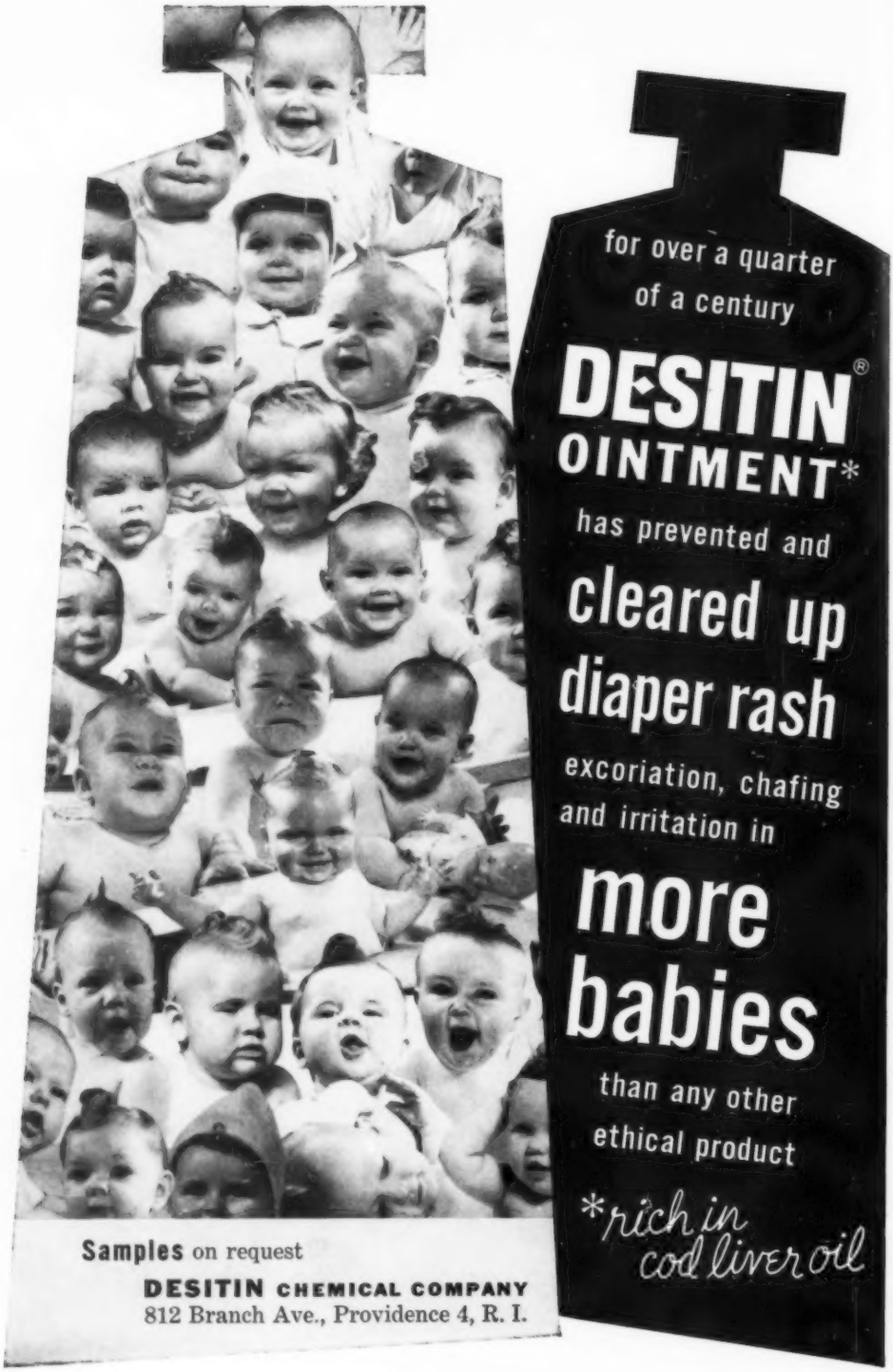
Literature on request *Detroit 11, Michigan*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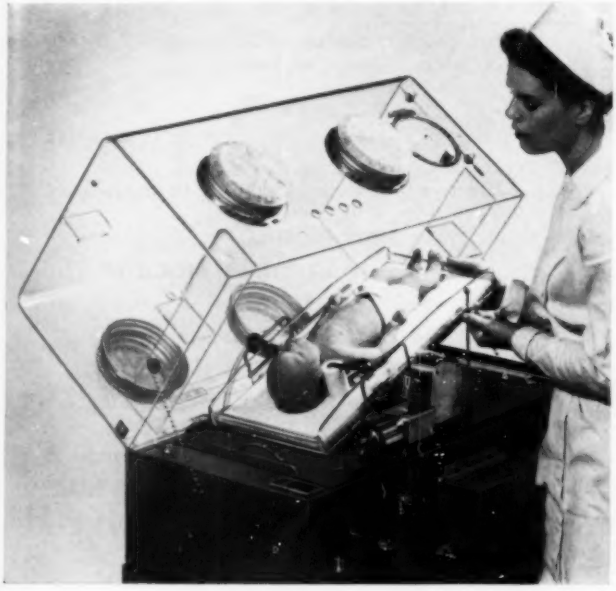

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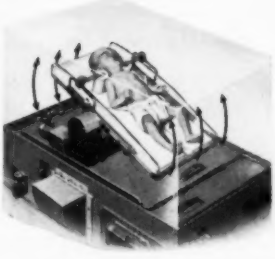

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*Lewis Webb Hill, M.D., "Treatment of Eczema in Infants and Children," Journal of Pediatrics, Vol. 47, No. 6, Dec. 1955.

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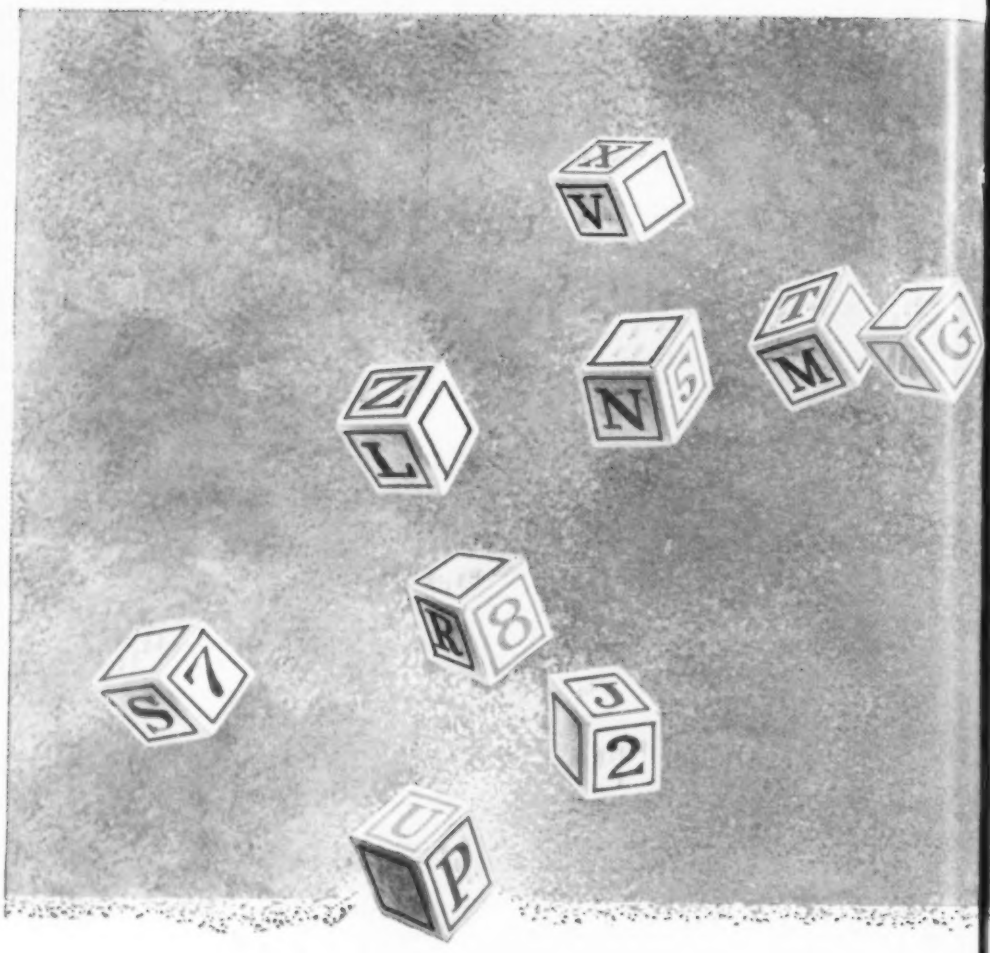

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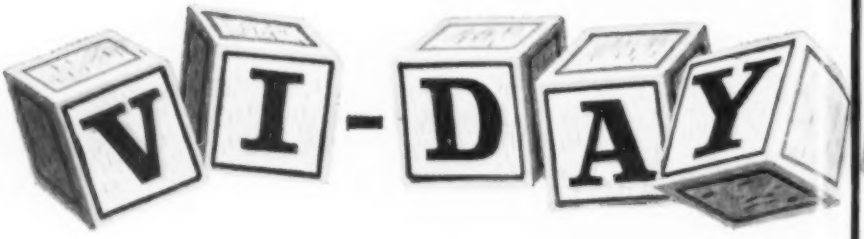

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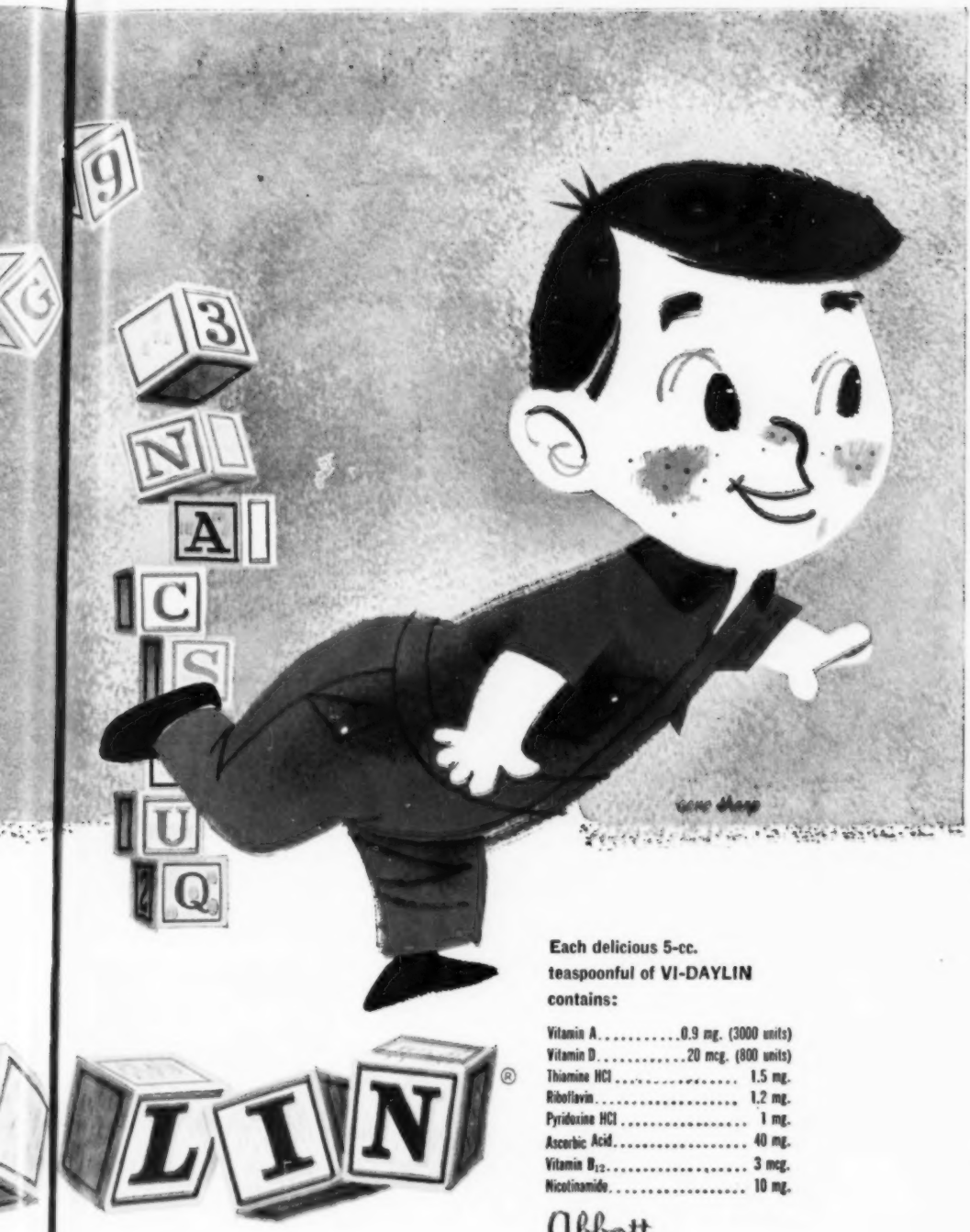

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Support where it's needed

...and room for toes to grow in

Foot Problems in Children

by A. Rubin, D.S.C.*

Mechanical foot problems in children are most likely to develop in two special periods. The first of these covers the early walking and preschool years. At this time the foot is first subjected to the forces of bodily weight and muscular force. Reflexes are being conditioned to achieve automaticity. Imitative stance and gait patterns are re-enforcing or modifying hereditary tendencies. The automaticity of walking and the flat surfaces we tread on, tend to produce localized instead of dispersed stress pathways. The rate of growth at this age is rapid.

The other period extends through pubescence and into adolescence. Here the growth rate is again accelerated. Hormonal out-pourings are being adjusted at new levels. New social and physical demands affect the physique as well as the psyche.

The variations are mostly in degree and not in kind. A basic set of factors underlies all pathomechanical problems. When stresses are generated in a structure, reactions follow. In biological systems the reactions are modified by adaptive responses tending to maintain the "steady state." A pathomechanical foot problem is a significant deviation. The involved structure (its osseo-ligamentous architecture and its working postural attitude) has been unable to adjust satisfactorily to the forces (stressors) imposed upon it.

The etiologic factors, then, may be classified in three groups:

1. STRUCTURE. — Certain variations of bony alignment and/or morphology provide poor stress resistant patterns. Some of these are short or hypermobile first metatarsal segment,[2] scanty sustentaculum tali,[3] tarsal coalitions,[3] "gorilloid" navicular, increased sub-talar declination, ligamentous shortcomings, etc.

2. STRESSORS. — Hard, flat walking surfaces, poor stance and gait habits, systemic disorders, footgear failure and work-load are some of the affecting causes. Adults, of course, are subject to many more, but these are the major stresses in children.

3. STRESS ADAPTATION (AFTER SELYE[4]). — Adequate adaptation means good health. Hypo- or hyperadaptation may mean the converse. In the child, the endocrine aspect of this has only slight application. The neuromuscular apparatus, however, is a potent force, particularly the way the leg muscles distribute stresses generated in the foot.

This concept enables the setting up of a three-pronged attack. Quantitative assessment will depend on judgment. However, generally speaking, poor stress resistant patterns can be supported by use of proper shoes, wedges, pads, inserts, appliances, etc., until adequate adaptive changes and mechanisms make their further use unnecessary.

Stressors such as poor stance and gait can be reduced or eliminated by means of remedial and resistive exercises. Poor footgear can be discarded and proper footgear used to minimize the harmful effects of flat underfooting.

The neuromuscular aspect of stress adaptation can be directed, controlled, and assisted by use of specific exercises, wedges, appliances, or other devices.

Summing up, we can generalize that adequate treatment of a mechanical foot-problem consists of supporting the weak structure, eliminating or minimizing stressors, and assisting the body to adapt successfully.

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3. Harris, R. I. and Beath, T.: Army Foot Survey; an Investigation of Foot Ailments in Canadian Soldiers. Ottawa, 1947. (N.R.C. No. 1574).
4. Selye, H.: The Story of the Adaptation Syndrome. Montreal, Acta, Inc., 1952.

*Secy., Nat. Assoc. Chiropodists and Editor of its Journal. Formerly Director, Foot Clinics, and Prof. and Chief, Orthopedic Dept., Illinois College of Chiropody and Foot Surgery

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1. Siver, Robert H.: Current Medical Digest, Vol. XXI, No. 9, September 1954.
2. McGivney, John: Texas State Journal of Medicine, Vol. 51, No. 1, January 1955.
3. Frykman, Howard M.: Minnesota Medicine, Vol. 38, No. 1, January 1955.

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Tempra Drops—15 cc. bottles with calibrated 'Safti-Dropper'—60 mg. (1 grain) N-acetyl p-aminophenol in each 0.6 cc. (*wild-cherry-flavored*, red solution).

Tempra Syrup—8 fl. oz. bottles—120 mg. (2 grains) N-acetyl p-aminophenol per teaspoon (*mint-flavored*, green solution).

Dosage (orally, every 4 to 6 hours, as needed): 0 to 1 year, 60 mg.; 1-4 years, 60-120 mg.; 4-8 years, 120-240 mg.; 8-12 years, 240 mg.

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SYMBOL OF SERVICE IN MEDICINE

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1. *An ideal food for milk allergies, eczema and problem feeding*
2. *An excellent formula for regular infant feeding*

Strikingly similar to mother's milk in composition and ease of assimilation, babies thrive on SOYALAC.

Clinical data furnish evidence of SOYALAC'S value in promoting growth and development.

Protein of high biologic value is obtained from the soybean by an exclusive process.

SOYALAC is an ideal "regular" formula. It also helps solve the feeding problems of prematures and infants requiring milk-free diets.

No mixing problem with SOYALAC Concentrated Liquid. Simply dilute with equal amount of water.

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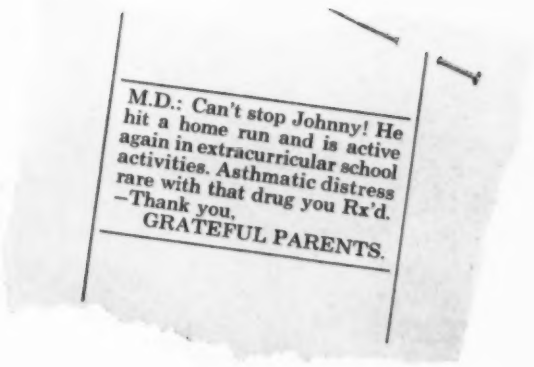
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Most active corticoid; minimal disturbance of electrolyte balance. White, scored 5 mg. tablets (bottles of 20 and 100) and pink, scored 1 mg. tablets (bottles of 100).

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SQUIBB IRON, B COMPLEX AND B_{12} VITAMINS ELIXIR

- to correct many common anemias
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Squibb Quality—
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Each teaspoonful (5 cc.) supplies:

Elemental Iron (as ferric ammonium citrate and colloidal iron) (equivalent to 130 mg. ferrous sulfate exsiccated)	38 mg.
Vitamin B_{12} activity concentrate	4 mcg.
Thiamine mononitrate	1.0 mg.
Riboflavin	1.0 mg.
Niacinamide	5 mg.
Pantothenic acid (Panthenol)	1.5 mg.
Pyridoxine hydrochloride	0.5 mg.

Alcohol content: 12 per cent

Dosage: 1 or 2 teaspoonfuls t.i.d.

Supply: Bottles of 8 ounces and 1 pint.

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NEOMYCIN
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in the unique FUZENE® base which releases high antibiotic concentrations not obtained with grease-base ointments

Here is visible evidence that Neo-Polycin releases more antibiotics than grease-base ointments. Compare the zones of inhibition of Staph. aureus by Neo-Polycin (in the Fuzene base) and product A—a grease-base ointment.

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Beech-Nut APPLE SAUCE
Real apples coming up, Junior – natural taste, natural vitamins in Beech-Nut
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NEW INTRAMUSCULAR IRON PROVIDES PRECISION THERAPY, PROMPT RESPONSE

IMFERON,® the new intramuscular iron-dextran complex, was introduced to American hematologists at the Sixth International Congress of the International Society of Hematology held in Boston, August 27 to September 1, 1956. Recent experience from over 6 million injections has shown that this iron preparation is easy to administer, notably free from toxic effects, quickly absorbed and productive of rapid hematologic and clinical improvement. It has been termed "...the only therapeutically effective iron preparation for intramuscular use...."[1]

IMFERON meets the need for a safe, effective agent when parenteral iron is preferable for patients with iron deficiency anemia who are resistant or intolerant to oral iron, those with depleted iron reserves and those who require rapid restoration of hemoglobin, *e.g.* last trimester of pregnancy.

Previous parenteral iron preparations were unsatisfactory because of toxicity, pain on injection, or because they contained insufficient iron. **IMFERON** contains the equivalent of 5 per cent elemental iron. It is more stable than iron saccharate both *in vitro* and *in vivo* and does not precipitate in plasma over a wide pH range. It is isotonic with tissue fluids and has a pH of 5.2 to 6.0[1] Utilization for hemoglobin formation is almost quantitative.

Precision Therapy with IMFERON: Before treating a patient with **IMFERON**, total iron requirement is calculated by formula or determined from a convenient dosage chart. Then appropriate amounts of **IMFERON** are injected daily or every other day, until the total calculated required amount is given.

Iron Deficiency Anemia of Infancy: IMFERON provides a convenient safe means for restoring hemoglobin levels and iron reserves in anemic infants. Excellent results were obtained by Gaisford and Jennison[2] with **IMFERON** in 100 iron-deficient infants. From a pretreatment average of 54.5 per cent, hemoglobin levels rose to 87 per cent 10 weeks after the start of therapy. Clinical improvement paralleled this response. Premature infants and surgical cases were similarly benefited. **IMFERON** gave "...all the advantages of transfusion or intravenous therapy without the disadvantages."[2] There were no side effects in any of the infants treated. Wallerstein[3] confirmed these results, furnishing evidence that **IMFERON** is well absorbed and appears in the bone marrow 12 to 24 hours after injection. Results are equal to those with intravenous saccharated iron oxide without the unpleasant side effects. Sturgeon[4] showed that the first year's iron requirements in infancy can be supplied with three injections of **IMFERON.**

Iron Deficiency Anemia of Pregnancy: Nausea precludes oral iron therapy in many anemic pregnant women. In those with severe anemia who are first seen late in pregnancy, prompt hemoglobin regeneration is unobtainable with oral iron. **IMFERON** produced prompt hemoglobin responses in anemia of pregnancy,[5,6] the results being similar to those obtained with intravenous saccharated iron oxide. Side effects were virtually absent with **IMFERON.**[5,6]

Resistant Hypochromic Anemia: Patients who do not respond to oral iron, those who cannot take oral iron and those with gastrointestinal pathology respond well to injections of **IMFERON.**[7-11] While oral iron is of little value in treating the anemia of rheumatoid arthritis, **IMFERON** is "...as beneficial as intravenous iron and easier to administer."[9]

Present Studies: Published reports and recent findings of clinical investigators confirm the effectiveness and safety of **IMFERON** for hemoglobin regeneration and creation of iron stores. More than 70 studies are now being completed in the United States. Reports stress prompt hemoglobin response, ease of administration and freedom from side effects. Clinicians desiring additional information should request Brochure No. NDA 17, **IMFERON,** Lakeside Laboratories, Inc., Milwaukee 1, Wisconsin.

References: (1) Brown, E. B., and Moore, C. V., in Tocantins, L. M.: Progress in Hematology, New York, Grune & Stratton, Inc., 1956, vol. I, p. 25. (2) Gaisford, W., and Jennison, R. F.: Brit. M. J. *2*:700 (Sept. 17) 1955. (3) Wallerstein, R. O.: J. Pediat. *49*:173, 1956. (4) Sturgeon, P.: Pediatrics *18*:267, 1956. (5) Jennison, R. F., and Ellis, H. R.: Lancet *2*:1245 (Dec. 18) 1954. (6) Scott, J. M., and Govan, A. D. T.: Brit. M. J. *2*:1257 (Nov. 27) 1954. (7) Grunberg, A., and Blair, J. L.: A.M.A. Arch. Int. Med. *96*:731, 1955. (8) Millard, J. B., and Barber, H. S.: Ann. Rheumat. Dis. *15*:51, 1956. (9) Baird, I. M., and Podmore, D. A.: Lancet *2*:942 (Nov. 6) 1954. (10) Cappell, D. F.; Hutchinson, H. E.; Hendry, E. B., and Conway, H.: Brit. M. J. *2*:1255 (Nov. 27) 1954. (11) Stevens, A. R.: A.M.A. Arch. Int. Med. *96*:550 1956.

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for rapid eradication of infection

In the majority of 112 cases of acute, persistent or relapsing urinary tract infections "nitrofurantoin [FURADANTIN] was effective clinically, with a pronounced improvement, indicated by the appearance of the urine as well as by verbal commendation by the patient, within 24 to 36 hours . . . Some of these patients with seemingly impossible cases were cured of their infection."*

FURADANTIN *first* because of these advantages: a specific for urinary tract infections • rapid bactericidal action • negligible development of bacterial resistance • nontoxic to kidneys, liver and blood-forming organs.

AVERAGE DOSAGE: *ADULTS*—four 100 mg. tablets daily; 1 tablet during each meal and 1 on retiring, with food or milk. In acute, uncomplicated infections, 50 mg. q.i.d. may be prescribed. If patient is unresponsive after 2 to 3 days, increase dose to 100 mg. q.i.d.

CHILDREN—5 to 7 mg. per Kg. (2.2 to 3.1 mg. per lb.) per 24 hours.

SUPPLIED: Tablets, 50 and 100 mg. Oral Suspension (25 mg. per 5 cc. tsp.).

*Stewart, B. L., and Rowe, H. J.: J. Am. M. Ass. **160**:1221, 1956.

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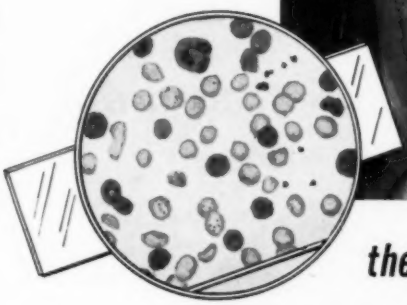

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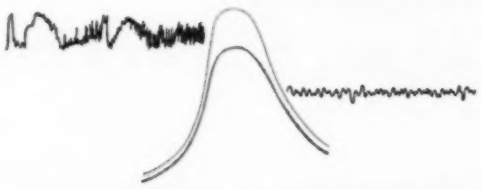

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". . . after the proper dose was established, 'Mysoline' was well tolerated without [serious] side effects."[3]

1. Doyle, P. J., and Livingston, S.: J. Pediat. *43*:413 (Oct.) 1953.
2. Livingston, S., and Petersen, D.: To be published.
3. Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.

LITERATURE ON REQUEST

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Suspension, 0.25 Gm. per 5 cc. (teaspoonful). Bottles of 8 fluidounces.

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GITALIGIN in a pleasant tasting form

Now whenever any of your little patients require digitalis therapy, give them GITALIGIN DROPS.

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Gitaligin Tablets;
0.5 mg. scored, in bottles of 30 and 100.

1. Am. Heart J. **52**:300 (Aug.) 1956.
2. Ann. Int. Med. **40**:820 (Apr.) 1954.
3. Am. J. M. Sc. **227**:188 (Feb.) 1954
4. Ann. Int. Med. **39**:1189 (Dec.) 1953.
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9. New Eng. J. Med.**246**:225 (Feb.) 1952.
10. Am. Heart J. **42**:292 (Feb.) 1951.
11. Fed. Proc. **9**:256 (Mar.) 1950.

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"... unusually satisfactory in the routine care of the skin of infants ... prophylactically effective in minimizing the incidence of diaper rash and miliaria."*

*Glaser, J.; Thompson, M. L., and Benson, T. D.: A.M.A. Am. J. Dis. Child. 81:329, 1951.

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Unlike many other lotions, Johnson's Baby Lotion forms a discontinuous protective oil film – not an impenetrable barrier. It contains hexachlorophene (0.5 per cent) – for potent, persistent bacteriostatic-bactericidal action. Routine use minimizes irritations – betters skin care.

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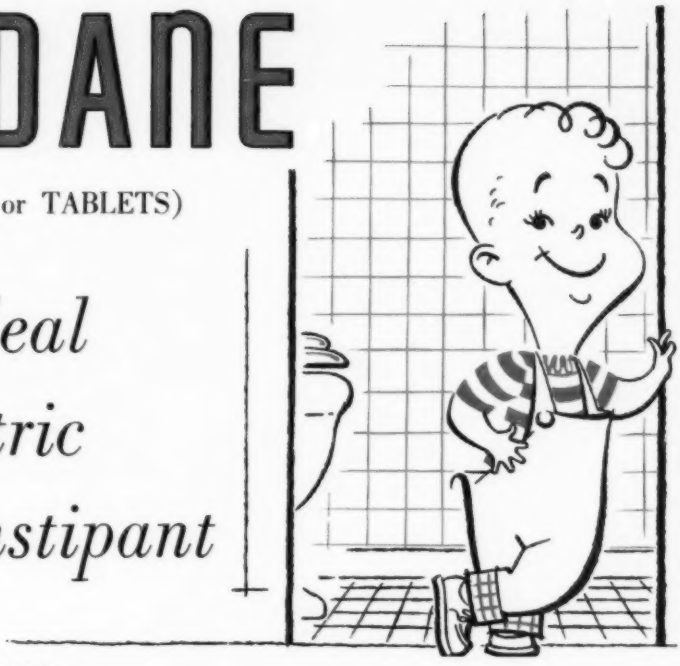

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Safety First | in emesis therapy

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SAFE

EMETROL will not suppress symptoms arising from organic etiology. It controls vomiting of functional origin quickly.

Dosage: Adults, 1 or 2 tablespoonfuls; infants and children, 1 or 2 teaspoonfuls, as often as every 15 minutes. Always administer *undiluted,* and forbid oral fluids for at least 15 minutes after each dose. Even if first dose is not retained, continue administration. If vomiting is not controlled within one or two hours, look for organic etiology. For individual dosage regimens in various indications, please send for literature.

1. Bradley, J. E.: Mod. Med. 20:31, No. 20, 1952.

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AMMENS® gives soothing protection to babies' tender skin. And when diaper rash, prickly heat or other skin irritations make him restless, AMMENS eases discomfort, promotes healing.

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1. Cornely, D. A., and Ritter, J. A.: N-acetyl-p-aminophenol (Tylenol Elixir) as a Pediatric Antipyretic-Analgesic, J.A.M.A. *160*:1219 (Apr. 7) 1956.

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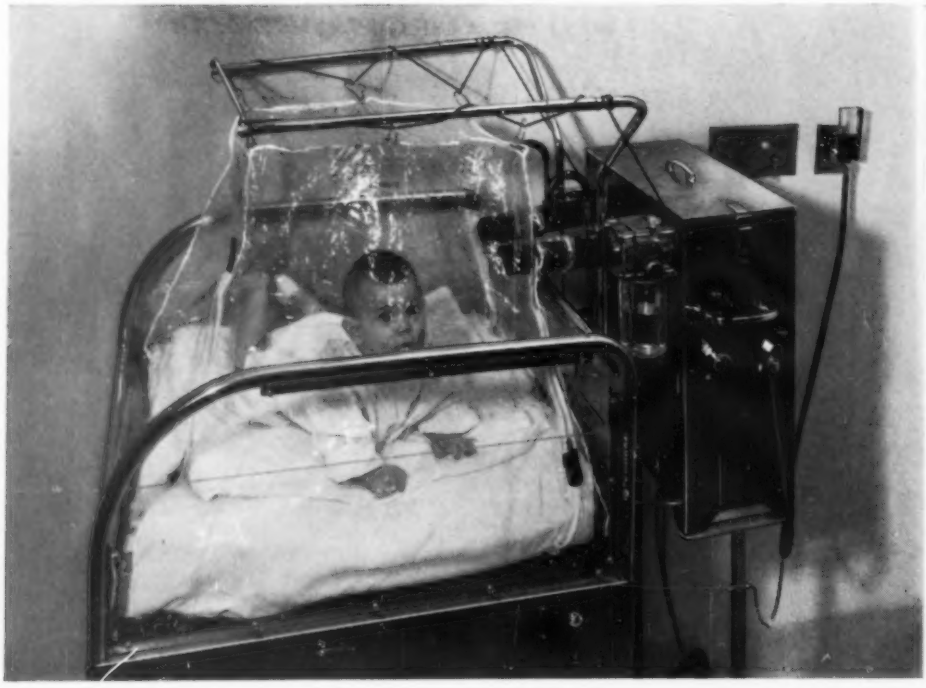

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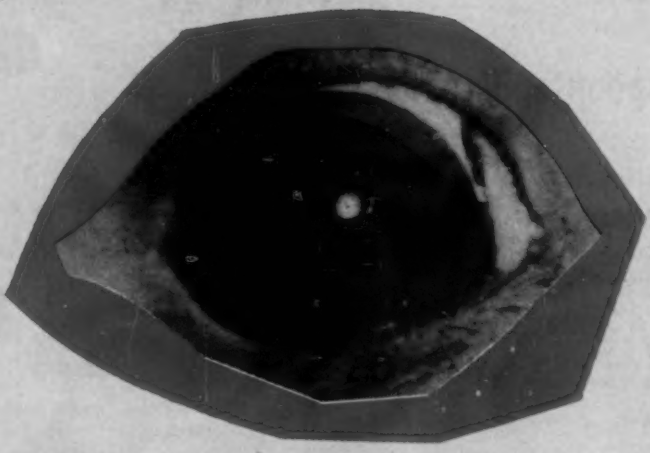

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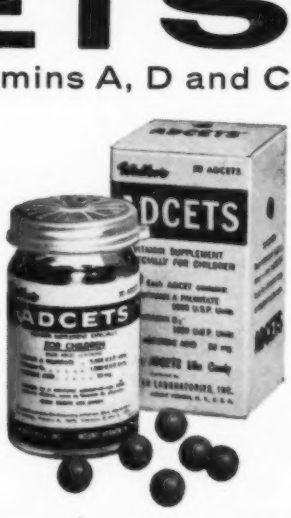

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1. Goldstein, Louis S., Clinical Medicine *59*:455 (1952).

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1. Goodman, L., and Gilman, A.: Pharmacological Basis of Therapeutics, New York, Macmillan, 1955, p. 1153. 2. Brown, H. W., et al: J. A. M. A. *161:* 515 (June) 1956. 3. Hoekenga, M. T.: World Med. J. *3:* (Sept.) 1956.

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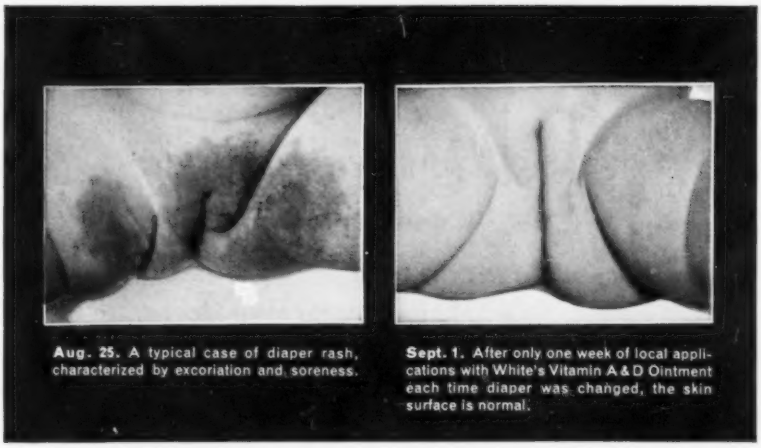

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1. Jackson, P. L.: Iron Deficiency Anemia in Infants, Editorial, J.A.M.A. *160*:976 (Mar. 17) 1956.

2. Martin, E. A.: Roberts' Nutrition Work with Children, Chicago, The University of Chicago Press, 1954, p. 211.

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June, 1957

A
SYMPOSIUM ON RHEUMATOID ARTHRITIS

Guest Editor, Joseph J. Bunim, M.D.

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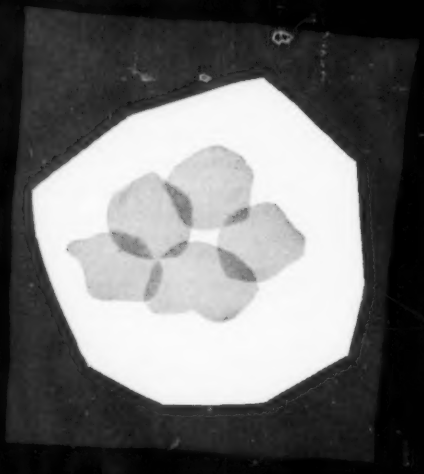

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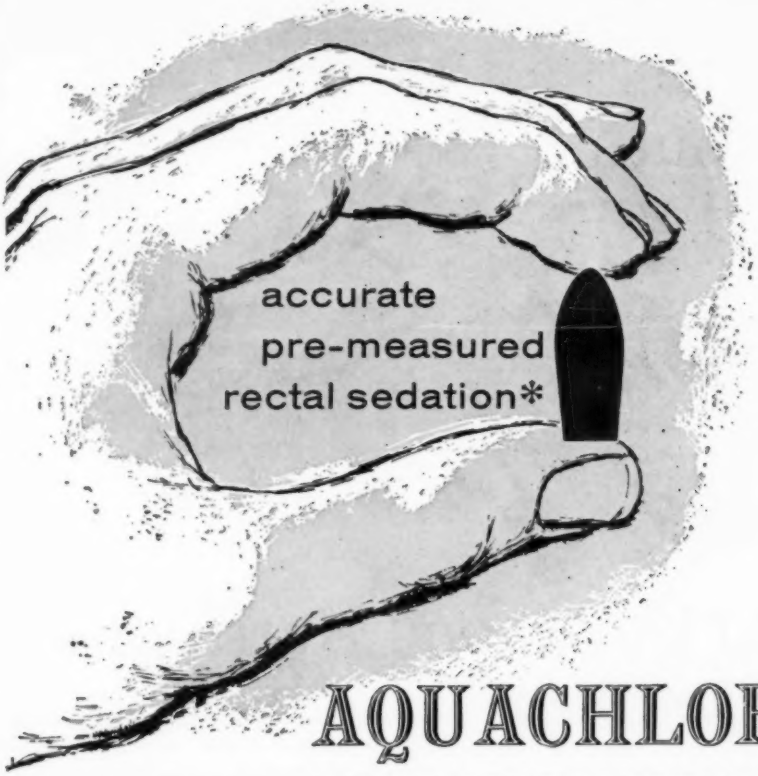

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These are some of the reasons why the role of enriched bread, in improving the health of millions of American school children, has been referred to as one of the most important advancements in public health measures since compulsory pasteurization of milk.

1. Martin, E.A.: Roberts' Nutrition Work with Children, Chicago, University of Chicago Press, 1954, p. 53.
2. Sebrell, W.H.: Developing Modern Nutrition Programs, Public Health Reports, United States Department of Health, Education and Welfare *69*:277 (Mar.) 1954.
3. Joint Report of the Council on Dental Health and the Council on Dental Therapeutics of the American Dental Association: Sugar and Dental Caries: The Effect on the Teeth of Sweetened Beverages and Other Sugar-Containing Substances, J. Am. Dent. A. *47*:387 (Oct.) 1953.

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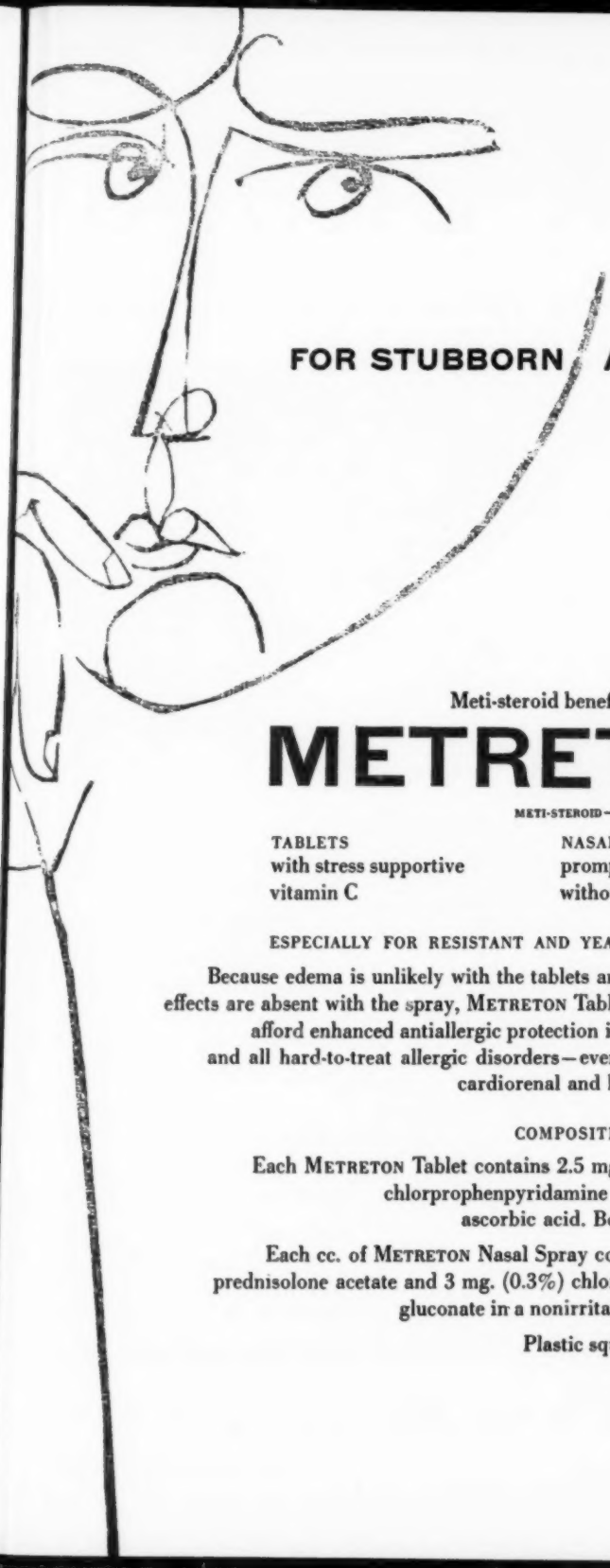
The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.



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Shwachman, H., The Child in Health and Disease, Grulee and Eley, 2nd Edit.

Shwachman, H. and Leubner, H., Advances in Pediatrics, VII, 249, 1955.

Kagan, B. M., Illinois Medical Journal, 107, 120, 1955.

Kumar, B. B., and Gibbs, G. E. A.M.A. Journal Diseases of Children, 91:606, 1956.

Literature on request.

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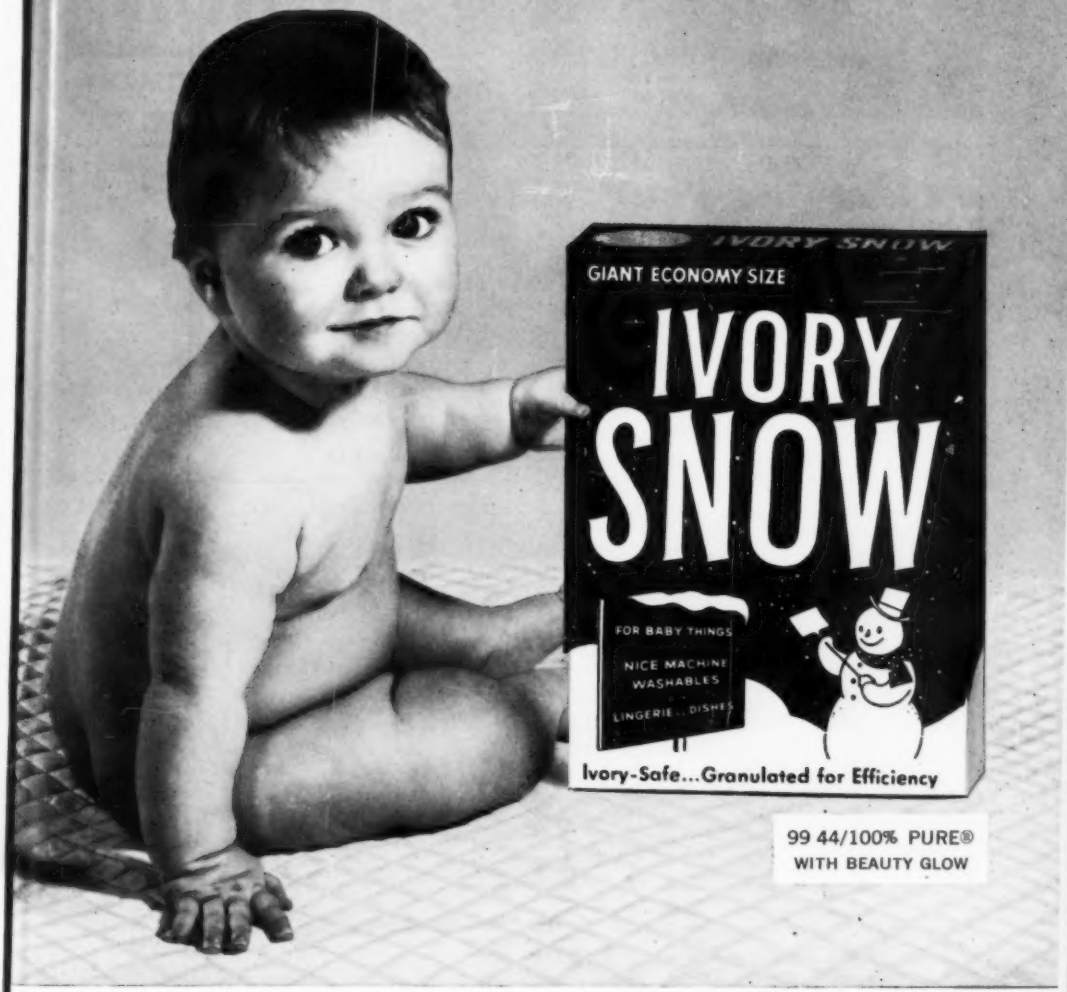

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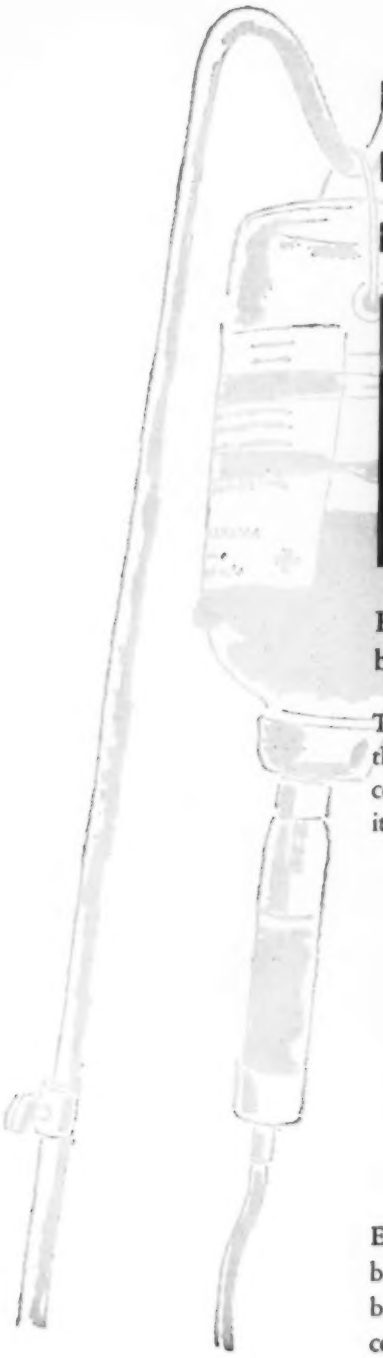

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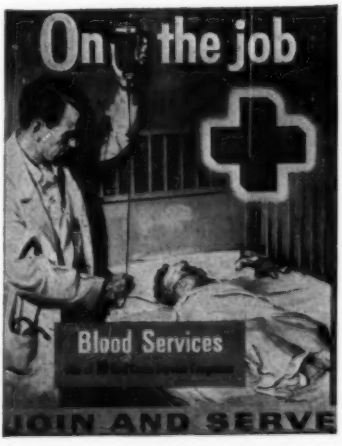

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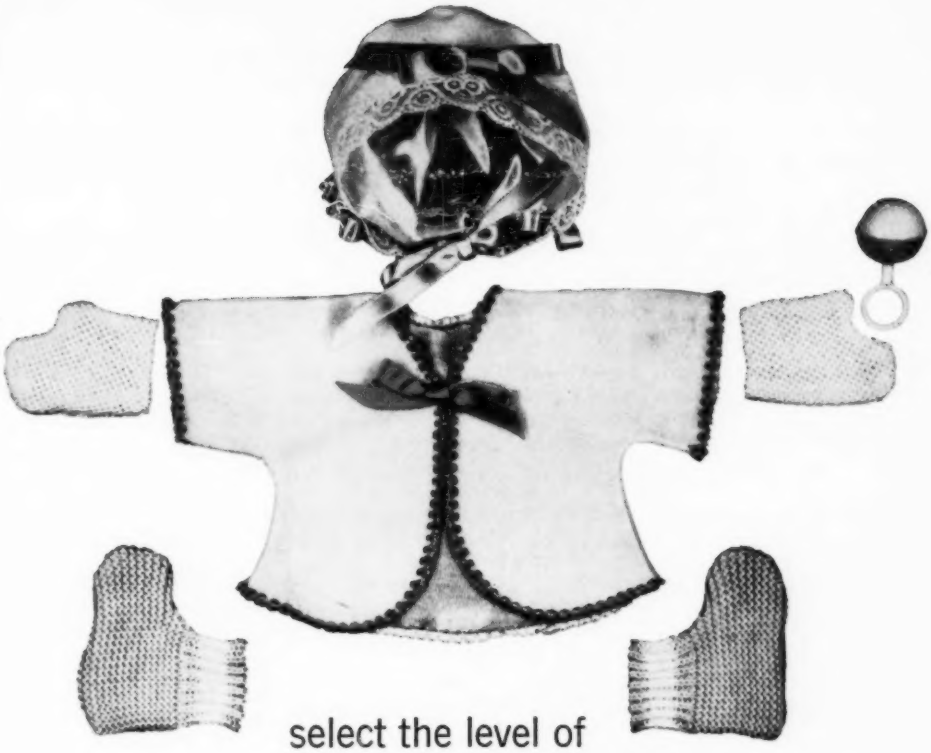

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